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Portocaval Anastomosis and Hepatic Encephalopathy: A Narrative Review

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ABSTRACT

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome resulting from liver failure, cirrhosis, or portosystemic shunting, and is characterized by cognitive, behavioral, motor, and sleep disturbances. Portocaval anastomosis (PCA) has emerged as a robust and reproducible experimental model of type B HE, allowing the study of brain disturbances associated with chronic portosystemic shunting. Since its adaptation to rodents, PCA studies have revealed sustained metabolic dysfunction, persistent hyperammonemia, and marked neurochemical alterations, contributing to a shift in the understanding of HE from a reversible metabolic disorder to a multifactorial and neurological condition.

Keywords: PCA; Portacaval Shunt; End-To-Side Portacaval Anastomosis

Abbreviations: HE: Hepatic Encephalopathy; PCA: Portocaval Anastomosis; GFAP: Glial Fibrillary Acidic Protein; LTP: Long-Term Potentiation; PV: Portal Vein; CV: Cava Vein

Introduction

Hepatic encephalopathy (HE) is a complex neuropsychiatric disorder arising from liver failure, cirrhosis, and/or portosystemic shunts. A major consequence of hepatic dysfunction is impaired detoxification of ammonia derived from intestinal metabolism, leading to elevated circulating levels of this neurotoxin, which readily crosses the blood-brain barrier and accumulates in the brain, triggering neurochemical and cellular disturbances that disrupt normal neuronal function [1]. Because of these alterations, HE is clinically characterized by a broad spectrum of neurological manifestations, including cognitive impairment, behavioral

and personality changes, psychomotor abnormalities, and sleep–wake disturbances [2]. According to the degree and severity of liver failure, disease or impairment HE has been classified into three different types. Type A, associated with acute liver failure; type B, related to portosystemic shunts in the absence of intrinsic liver disease; and type C, occurring in chronic liver disease [3]. Within this framework, portocaval anastomosis (PCA) has been established as a robust experimental model of type B HE, reproducing key neurochemical, synaptic, cognitive, and motor features of the disorder.

The Portocaval Anastomosis Model: Early Characterization

From the mid twentieth century onward, PCA became one of the most relevant experimental models for the study of HE. The procedure was first performed in dogs by Nikolai Vladimirovich Eck in 1877 and, eighty-four years later, was adapted to the rat by Lee and Fisher, who established a reproducible and technically reliable model. This surgical approach consists of an end-to-side anastomosis between the portal vein and the inferior vena cava, diverting portal blood flow away from the liver and directly into the systemic circulation (Figure 1), [4,5]. Early investigations focused on describing the systemic consequences of chronic portal blood flow diversion. These studies reported that PCA was initially associated with body weight loss, hepatocellular injury, and early biochemical alterations, which were subsequently accompanied by marked hemodynamic changes, including a reduction in effective hepatic blood flow, compensatory redistribution of arterial flow, and an increase in cardiac output [5-7]. With time, these alterations were shown to evolve into a chronic hepatic metabolic dysfunction characterized by a predominantly catabolic profile, including hypoglycemia, hyperglucagonemia, reduced lipogenesis, increased lipolysis, and decreased synthesis of cholester-

ol and bile acids, indicating a sustained disruption of systemic lipid metabolism [8,9].Concurrently, it was established that the hepatic atrophy observed after PCA was not attributable to a reduction in hepatic blood flow per se, but rather to portal blood diversion and the consequent loss of trophic factors, as the liver retained its regenerative capacity [10,11].

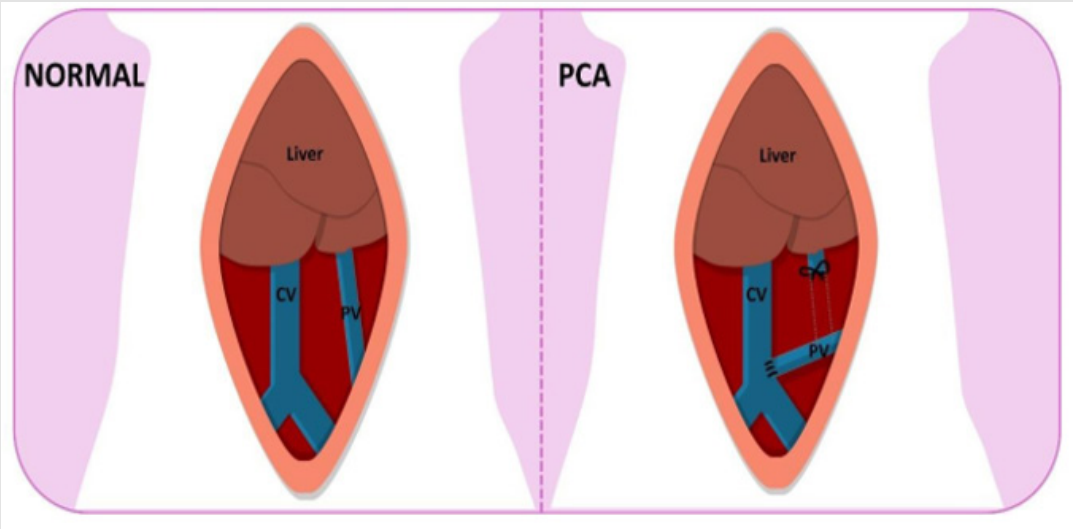

Figure 1: Portocaval anastomosis in the rat. Schematic representation of the surgical procedure showing the cava vein (CV) and portal vein (PV). Comparison between normal and portocaval anastomosis (PCA) rats.

Subsequently, during the early 1980s, further studies demonstrated that portosystemic derivation induces a profound reorganization of hepatic microcirculation, characterized by abnormal arterialization of the sinusoidal bed and structural and functional alterations of the endothelium and Kupffer cells. These findings consolidated the concept that PCA produces a complex and sustained hepatic dysfunction [12]. Collectively, this body of work established PCA as a robust and reproducible experimental model of chronic liver dysfunction and its systemic consequences, thereby laying the groundwork for the subsequent identification of one of its most relevant extrahepatic effects, hyperammonemia.

Hyperammonemia in PCA Model

During the 1970s, it was shown that this model induces a progressive increase in brain ammonia levels, accompanied by alterations in glucose metabolism and in amino acid homeostasis, particularly glutamate and aspartate, as well as changes in the cytoplasmic redox state and a reduction in ATP content [13,14]. Despite these metabolic disturbances, the overall cerebral energy status appeared to be relatively preserved. Later studies using magnetic resonance spectroscopy demonstrated that key energetic metabolites, including ATP, phosphocreatine, ADP, AMP, and intracellular pH, remain stable even after acute ammonia intoxication. These observations suggested that the cerebral dysfunction induced by PCA depends primarily on specific neurochemical alterations affecting neurotransmission and amino acid metabolism rather than on a generalized failure of brain energy metabolism [15]. As research advanced, the mechanisms underlying persistent cerebral hyperammonemia began to emerge. Although systemic redox alterations have been described [16]. Yang, et al. [17] found no evidence of oxidative stress in the frontal cortex four weeks after PCA, suggesting that elevated brain ammonia does not necessarily lead to overt oxidative damage. Regarding ammonia detoxification, Butterworth [18] reported a partial reduction of glutamine synthetase activity in the cerebral cortex, limiting local ammonia clearance, while activity remained normal in the brainstem. Later, Girard and Butterworth [19] showed that PCA causes hepatic atrophy with loss of liver glutamine synthetase, whereas activity is preserved in the brain and increased in skeletal muscle, indicating that muscle serves as an alternative site for ammonia detoxification. Together, these findings reveal tissue-specific regulation of glutamine synthetase and help explain the vulnerability of the brain to hyperammonemia after anastomosis.

Subsequently, studies began to focus on the sources of ammonia reaching the brain in this model. Jeppsson, et al. [20] reported that both germ-free and conventionally raised PCA rats developed hyperammonemia, along with changes in plasma and brain amino acid profiles, such as increased aromatic amino acids and greater transport of tryptophan into the brain, while branched-chain amino acids were unchanged. These results showed that these metabolic alterations occur independently of intestinal bacterial activity. Consistent with this,

Romero Gómez, et al. [21] demonstrated that portosystemic shunting increases the expression and activity of phosphate-activated glutaminase in brain regions including the cortex and basal ganglia, leading to enhanced local ammonia production. Together, these findings indicate that brain ammonia accumulation in PCA results not only from increased systemic levels but also from region-specific metabolic processes within the brain.

Astrocytic and PCA-Induced Hyperammonemia

From the earliest neuropathological descriptions of HE, astrocytes were recognized as one of the primary cellular targets affected in the PCA model. In the late 1970s, Doyle, et al. [22] demonstrated that this procedure induced nuclear alterations in rat astrocytes that closely resembled those observed in patients with HE. In line with these observations, earlier studies had already reported that the model consistently reproduced Alzheimer type II astroglia changes characteristic of hepatic disease. These alterations correlated with plasma ammonia levels, were partially reversible, and were interpreted as an adaptive metabolic response of astrocytes to increased cerebral glutamine, thereby reinforcing the concept of hyperammonemia as a central driver of astroglia dysfunction [5]. During the 1980s and early 1990s, research efforts gradually shifted toward understanding the functional implications of these structural abnormalities. In this period, PCA was shown to profoundly disrupt glutamate metabolism, leading to increased extracellular glutamate release as a consequence of astroglia dysfunction. Butterworth, et al. [23]. demonstrated that this process induced compensatory changes in glutamatergic receptors and contributed to the impairment of excitatory neurotransmission observed in HE. In parallel, Swain, et al. [24] provided direct evidence that this experimental condition induces elevations in intracellular pH and astrocyte volume. These changes were linked to intracellular glutamine accumulation and disturbances in ionic homeostasis, establishing astrocyte swelling as a central event in the pathophysiology of PCA-induced HE. Subsequent studies revealed that the astroglia response to portal-systemic diversion exhibited marked regional and cellular heterogeneity. Suárez, et al. [25] showed that chronic PCA induced a differential response in the cerebellum, characterized by increased expression of glial fibrillary acidic protein (GFAP) in Bergmann glial cells, particularly within layers associated with glutamate release. In contrast, astrocytes displayed reduced GFAP immunoreactivity compared with control animals. The absence of changes in vimentin expression suggested that PCA selectively modifies the GFAP dependent astroglia cytoskeleton without inducing widespread glial activation, pointing to a region-specific response whose molecular mechanisms were not yet understood.

In the early 2000s, this concept was further refined by studies examining the impact of hyperammonemia on astrocytic structural integrity. Bélanger, et al. [26] demonstrated that acute in vivo hyperammonemia produced a marked reduction in GFAP expression at both the mRNA and protein levels in the brain, while leaving other glial proteins, such as S-100β, unaffected. This loss of GFAP was associated with increased brain water content and elevated ammonia concentrations, providing additional evidence that disruption of the astrocytic cytoskeleton directly contributes to the development of cerebral edema in acute HE. Taken together, the historical progression of these findings established astrocytes as a central element in the pathophysiology of PCA-induced HE, integrating structural, metabolic, and functional alterations that link hyperammonemia to impaired neurotransmission, cellular swelling, and the development of cerebral edema.

Behavioral, Circadian, and Sleep Disturbances in the PCA Model of HE

The investigation of behavioral and sleep disturbances in the PCA model evolved gradually from the recognition that HE causes not only cognitive impairment but also neuropsychiatric alterations and disturbances. Within this framework, in the mid-1990s, De Waele, et al. [27] provided early evidence that this experimental procedure induces selective alterations in the cerebral opioid system. Specifically, they reported increased β-endorphin levels accompanied by a reduction in μ- and δ-opioid receptor expression, suggesting a state of chronic activation of the endogenous opioid system together with compensatory receptor downregulation. This mechanism was proposed as a contributor to alterations in behavior, mood, vigilance, and pain perception. Subsequently, Córdoba, et al. [28] shifted the focus toward a functional assessment of behavioral impairment by introducing the circadian rhythm of locomotor activity as an objective and reproducible marker of brain dysfunction. Their studies demonstrated that rats with PCA exhibited a marked disruption in the synchronization of locomotor activity with the light-dark cycle, whereas partial shunt stenosis attenuated these disturbances, closely paralleling clinical observations in patients with HE. Later, Lozeva, et al. [29] showed that blockade of histamine H1 receptors restored locomotor activity and improved circadian rhythm organization in rats with PCA, implicating a dysregulation of histaminergic neurotransmission. Consistent with this, both PCA in rats and HE in humans were later found to be associated with a selective upregulation of cortical histamine H1 receptors, supporting the concept that cortical histaminergic hyperactivity contributes directly to neuropsychiatric manifestations [30]. By the late 1990s, Lozeva, et al. [31] demonstrated that PCA induces persistent alterations in several monoaminergic systems, including serotonin, dopamine, and histamine, which were associated with both early and late neuropsychiatric features. More recent studies integrated these behavioral and neurochemical observations with direct assessments of sleep architecture. Notably, Llansola, et al. [32] reported that rats with PCA reproduce key sleep disturbances observed in patients with HE, including a progressive reduction in total sleep time and pronounced sleep fragmentation. These alterations were linked to hyperammonemia and neuroinflammation and involved serotonergic, hormonal, and glial mechanisms, further consolidating the PCA

model as a robust experimental framework for the integrated study of behavioral abnormalities, circadian rhythm disruption, and sleep disturbances.

Cerebral Edema and PCA in a Model of HE

Cerebral edema associated with PCA-induced HE was initially linked directly to hyperammonemia. However, during the 1990s, studies using this experimental model began to demonstrate that ammonia, although a necessary factor, was not sufficient on its own to explain the development of cerebral edema. In this context, Bosoi, et al. [33] demonstrated that brain edema developed only when hyperammonemia was combined with pharmacologically induced systemic oxidative stress, even though no oxidative damage was detected in brain tissue. Importantly, neither systemic oxidative stress alone nor hyperammonemia by itself was sufficient to induce cerebral edema. These findings indicated that cerebral edema arises from the interaction between hyperammonemia and systemic metabolic disturbances rather than from either factor alone. Concurrently, attention shifted toward the role of glutamine as an intracerebral mediator of edema in the PCA model. In this regard, Master, et al. [34] demonstrated that hyperammonemia-induced cerebral edema was largely dependent on glutamine synthesis within the brain. Inhibition of glutamine synthetase markedly reduced both cerebral edema and hyperemia, thereby establishing glutamine accumulation as a central mechanism linking ammonia metabolism to brain swelling in this experimental setting. More recently, the contribution of cerebral edema to neurological dysfunction has been reassessed in the context of disease severity. Cauli, et al. [35] showed that in mild chronic HE, cerebral edema does not play a major role in cognitive or motor impairment, redirecting the pathogenic focus toward synaptic dysfunction and neuroinflammatory processes. Taken together, the historical progression of these findings supports a dynamic, stage-dependent view of cerebral edema in PCA-induced HE, in which its relevance varies according to both the severity and temporal evolution of the disorder.

Behavioral deficits and synaptic dysfunction in the PCA Model of HE

Early behavioral studies in rats subjected to PCA demonstrated reproducible motor and cognitive impairments, even in the absence of severe structural liver damage [36,37]. Monfort, et al. [38] subsequently demonstrated that these impairments were potentially linked to a marked dysfunction of the glutamate–nitric oxide–cGMP pathway in the cerebellum, a signaling cascade essential for synaptic plasticity and learning processes. Shortly thereafter, Erceg, et al. [39] confirmed that disruption of this pathway is a direct determinant of hyperammonemia-associated cognitive impairment and showed that pharmacological restoration of cGMP levels normalizes learning performance, identifying this signaling pathway as a potential therapeutic target. These functional observations were further expanded by studies showing that glutamatergic dysfunction also compromises the organization of neuronal circuits. Cauli, et al. [40] demonstrated that reduced motor activity under conditions of portosystemic shunting is associated with excessive glutamate levels and abnormal activation of the metabotropic glutamate receptor mGluR1 in the substantia nigra pars reticulata, and that pharmacological blockade of this receptor reverses motor deficits. Subsequent studies revealed that, in this model, dopaminergic circuits regulating locomotion are partially replaced by glutamate-dependent pathways, thereby contributing to the characteristic motor disturbances [41].

Importantly, these alterations were shown not to occur in isolation but to be amplified by central inflammatory processes. Cauli, et al. [42] demonstrated that brain inflammation exacerbates cognitive dysfunction and that anti-inflammatory treatment restores the functionality of the glutamate–nitric oxide–cGMP pathway in the cerebral cortex, leading to normalization of learning. Consistent with these findings, Suárez, et al. [43] identified dysregulation in the expression of neuronal and inducible nitric oxide synthase isoforms in Purkinje cells and Bergmann glia, suggesting that abnormal nitric oxide production contributes to cerebellar damage and neurological impairment. Collectively, these studies established that altered glutamatergic and nitric oxide signaling, modulated by neuroinflammation, constitutes a central mechanism underlying neuronal dysfunction in this experimental model.

In parallel, alterations in other modulatory systems were identified. Ahboucha, et al. [44] demonstrated a significant increase in neurosteroids with positive modulatory effects on the GABA-A receptor, the normalization of which improves motor deficits, supporting the hypothesis of increased GABAergic tone in HE. Concordantly, Cauli, et al. [45] showed that hypokinesia is associated with elevated extracellular glutamate levels in the substantia nigra pars reticulata, secondary to reduced expression of glutamate transporters, and that anti-inflammatory treatment restores both glutamate transport and motor function. Subsequent studies further expanded the characterization of cognitive alterations in the PCA model, revealing deficits across specific domains of memory and learning. Méndez, et al. [46] described impairments in spatial memory, with a dissociation between reference memory and working memory, suggesting the involvement of distinct neurobiological mechanisms associated with portosystemic shunting. Later, the same authors demonstrated deficits in associative learning, primarily attributed to hyperammonemia-induced alterations in glutamatergic and histaminergic neurotransmission [47]. At the synaptic level, Monfort, et al. [48] provided direct molecular evidence for these deficits by demonstrating that hippocampal long-term potentiation (LTP) is abolished as a consequence of impaired glutamate-dependent signaling. Specifically, deficient activation of NMDA receptors was observed, limiting calcium influx required for CaMKII activation and for the phosphorylation and translocation of the AMPA receptor subunit GluR1, a process essential for synaptic strengthening and memory consolidation. Together, these findings established that the

cognitive deficits observed in chronic HE is rooted in synaptic and molecular alterations of the glutamate–nitric oxide–cGMP pathway, potentiated by hyperammonemia and neuroinflammation, yet potentially reversible through pharmacological interventions targeting this cascade. Finally, integrative reviews synthesized these results within a unified pathophysiological framework. Cauli, et al. [49] and Felipo [50] concluded that the cognitive and motor alterations associated with the PCA model, and HE are primarily explained by dysfunction of glutamatergic and GABAergic neurotransmission, with a central role for the NMDA–NO–cGMP pathway and basal ganglia–thalamocortical circuits. These authors further emphasized the functional reversibility of these alterations through pharmacological modulation of synaptic signaling and inflammatory processes.

Neuroinflammatory and Neurodegenerative Mechanisms in PCA-Induced HE

For decades, HE induced by PCA was regarded primarily as a functional and potentially reversible disorder. However, beginning in the second decade of the twenty-first century, accumulating experimental evidence began to redefine this paradigm by incorporating neuroinflammation and progressive cellular damage as central components of its pathophysiology. The studies that drove this conceptual shift demonstrated that cerebral neuroinflammation plays a direct causal role in the cognitive alterations characteristic of HE. Hernández Rabaza, et al. [51] showed that, in rats subjected to PCA, hippocampal neuroinflammation alters the expression of GABAergic and glutamatergic receptors, resulting in learning deficits. Importantly, these effects were reversible following treatment with sildenafil, indicating that inflammation predominantly disrupts synaptic signaling mediated by the nitric oxide–cGMP pathway rather than inducing direct metabolic toxicity.

In parallel, Butterworth [52] provided evidence that HE is accompanied by early astroglia dysfunction, characterized by reduced expression of glutamate transporters such as EAAT-2, decreased levels of astroglia cytoskeletal proteins including GFAP, microglial activation, increased concentrations of neurosteroids with GABAergic activity, and the presence of oxidative stress. Together, these findings positioned neuroinflammation as a central axis of pathogenesis.

Subsequently, Butterworth [53] demonstrated that microglial activation and central inflammation represent early events in the progression of HE and cerebral edema in the PCA model, and that their inhibition prevents neurological deterioration. Subsequent studies established a direct link between peripheral inflammation and central neuroinflammation in HE associated with PCA. Dadsetan, et al. [54] demonstrated that systemic inflammation induces cerebellar neuroinflammation, increases GABAergic tone, and impairs motor coordination and learning; these effects were reversed by TNF-α blockade.

In complementary studies, the same authors showed that peripheral inflammation also triggers hippocampal neuroinflammation, alters the expression of AMPA and NMDA receptors, and produces deficits in spatial memory, which were likewise reversible following anti–TNF-α treatment. Collectively, these findings consolidated the existence of a peripheral inflammation–brain axis in this model. In agreement with these observations, Agustí, et al. [55] neuroinflammation-mediated increases in cerebellar GABAergic tone constitute a direct determinant of motor incoordination in HE. Moreover, they showed that pharmacological elevation of cGMP attenuates cerebral inflammation and restores motor function, integrating inflammatory processes, neurotransmitter dysfunction, and altered intracellular signaling within a unified pathophysiological framework.

This concept was further reinforced by studies using chronic PCA models, which revealed a shift from initially reversible neuronal dysfunction toward sustained structural damage. López Cervantes, et al. [56] characterized cerebellar spongiform degeneration associated with cytotoxic edema, oxidative stress, and neuroinflammation, changes that were accompanied by persistent motor deficits and indicative of progressive impairment of neuronal integrity. Together, these observations strengthened the parallel between chronic HE and neurodegenerative processes by demonstrating that the pathology extends beyond synaptic dysfunction to include overt structural compromise of nervous tissue. Subsequently, the same authors elucidated the subcellular mechanisms underlying this damage, showing that cerebellar neurodegeneration is closely linked to mitochondrial dysfunction, sustained oxidative stress, and an imbalance in mitochondrial fission and fusion processes critical for neuronal survival and function. Disruption of this energetic and dynamic equilibrium leads to a state of chronic metabolic vulnerability that facilitates the progression of neuronal injury beyond synaptic failure [57].

Additionally, the hippocampus of PCA rats exhibited profound alterations in the neuronal substrate underlying cognitive deficits. Significant impairments in spatial learning and memory were associated with reduced neuronal density, decreased nuclear area, and thinning of the dentate gyrus layers. At the cellular level, these structural changes were accompanied by a reactive glial environment, evidenced by increased GFAP expression, together with a marked reduction in markers of axonal integrity and neuronal plasticity, such as neurofilament NF200 and neurabin II. Collectively, these alterations indicate a sustained loss of synaptic reorganization capacity and limited neuronal recovery, contributing to persistent cognitive dysfunction [58].

Conclusion

The PCA model has been essential in redefining HE as a chronic and progressive neurological disorder, extending beyond a reversible metabolic disturbance. Studies using PCA demonstrate that the interaction between hyperammonemia and inflammatory mechanisms leads to impaired neurotransmission, synaptic dysfunction,

mitochondrial failure, and progressive neuronal damage, resulting in persistent cognitive and motor deficits. By reproducing the temporal progression of HE from early functional alterations to structural brain injury across vulnerable regions, the PCA model provides a robust experimental framework for mechanistic studies and for the development of therapeutic strategies. Beyond ammonia-lowering approaches, this model supports emerging treatments aimed at reducing neuroinflammatory responses, preserving mitochondrial function, restoring synaptic plasticity, and promoting neuronal survival, offering new avenues for improving neurological outcomes in chronic liver disease.

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