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Amino acid metabolism and Hepatic Encephalopathy

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1. Introduction:

Liver, the biochemical center on body with its abnormality invites myriad of complications along. Hepatic encephalopathy (HE) is out amongst various clinical symptoms of failure of liver, characterized by simple to complex abnormalities in case of hepatic insufficiency. The neuropsychiatric disorder has wide ranged clinical manifestations ranging from mood alterations to coma in acute cases. Keeping such wide manifestations in view, on the basis of west haven criteria, HE is categorized into five types:

a. Grade 0: No major abnormalities detected and a score of 4 is allocated.
b. Grade 1: Unawareness, euphoria along with lethargy or apathy are the signs for grade 1, with a score of 3.
c. Grade 2: Disorientation and inappropriate behavior are amongst other signs in grade2, providing it a score of 2.
d. Grade 3: State of confusion along with unresponsiveness, and bizarre behavior are the traits of grade 3, sliding the score to 1.
e. Grade 4: At this severe stage of HE, patient usually become comatose and the score allocated to this is 0.

The wide range of such clinical symptoms is based on pathogenic and chronological criteria down the spectrum.

The consideration towards HE etiology has took some major turn in the past researches and established the role of certain factors like Ammonia, Inflammation, Infection in pathogenesis of HE. HE is as well seen in consideration of several metabolic impairments, along with the effect from different precipitating factors like hormonal influences like Insulin, Thyroid and like others have influenced the research of HE in their own way. The role of amino acids has always been crucial in all the metabolic pathways of the body along with the disturbances arising in body in a way or another finds their way back to disturbances in amino acid metabolism making them significant to undergo research with.

2. Insufficient Liver and Amino Acid Imbalance in Blood Plasma:

The role of liver is prime in metabolism of amino acids as well in urea synthesis. Catabolism of hepatic encephalopathic central toxin, ammonia plays a fundamental role in such imbalance. As ammonia through reaction with keto acids is converted to non-toxic transport amino acid metabolite, alanine (A, Ala), or glutamine (Q, Gln) formation from glutamic acid (E, Glu) via another route. Liver uses different components of metabolites in varying processes like carbon skeleton is used for gluconeogenesis while nitrogen is utilized in urea formation (F. Rossi-Fanelli et al., 1987).

A widely studied theory for HE stems from the imbalance in plasma levels of branched chain amino acids (BCAAs) and aromatic amino acids (AAAs) (Fischer et al. 1976). This theory provides essentially a ratio between three BCAAs i.e. Valine (V, Val); Isoleucine (I, Ile); Leucine (L, Leu) along with two AAAs i.e. Phenylalanine (F, Phe); Tyrosine (Y, Tyr) referred as Fischer's ratio. This ratio is suggested to be inversely proportional to HE, lesser the ratio, more is the severity of HE (Fischer et al. 1976).

Walshe and co-workers in 1953 reported the rise in majority of amino acids number in chronic liver disease. While, methionine (M, Met) and Tyr are reported to be high in in a study on liver disorder and hepatic encephalopathy patients (Wu et al., 1955). Amino acids are well classified as neuro-stimulators or can be neuro-inhibitor. Glu, and aspartate (D, Asp) are registered neurostimulators while Tryptophan (W, Trp), a precursor of serotonin is amongst inhibitory amino acids. HE patients are reported to have increased levels of trp (Albrecht and Jones 1999; Carpenedo et al. 1998), Histidine (H, His), histamine precursor (Lozeva et al. 2003; Trevisani et al. 1994). GABA, gamma-aminobutyric acid, a well-studied neuroinhibitory might as well play a role in HE pathology (Butterworth, 2003). Such amino acid imbalance may cause changes in cerebral functioning because of neurotransmitter alterations and also affect protein metabolism (Pardridge 1998).

2.1 Pathogenesis of Amino acid Imbalance in Plasma:

The crucial position that liver holds in between portal and systemic circulation, provides it with regulatory and homeostatic function for GI tract absorbed substrates. As liver is the main site for amino acid degradation, (Miller, 1962) might explain the high rise of certain amino acids in its insufficiency. In cirrhotic patients with portocaval shunt leading to reduced liver cell mass and can contribute to accumulation of AAAs in blood stream while Iwaski et al., 1980 challenged the rise of AAAs in blood and reported their normal levels in idiopathic portal hypertension. The mechanism, i.e. the effect of plasma amino acid imbalance, behind the development of HE in patients with acute or chronic liver failure, it is thought to be different (Jalan et al. 2003). However, the data regarding the differences in the amino acid balance between these patient groups is limited. Thus, endogenous break down of body mass, which could be caused due to rise of phe, tyr levels, (Rosen et al., 1977) might be regarded as a biomarker for HE establishment and is now a days commonly regarded as well.

Non-esterified fatty acids (NEFA) and serum albumin levels, biomarkers for liver damage are observed to be high in chronic liver disease patients. The rising NEFA and albumin can be contributed by trp, the only amino acid present in plasma either bound to albumin or in free state. The unbound trp is closely related to NEFA because of its ability to displace trp from albumin's binding site and exceed its availability in free form in blood plasma beyond 15%, marked physiological limit

(McMenamy and Oncley, 1958). A study by Mortiaux and Dawson, 1961 called for decreased serum albumin as mainly due to reduced synthesis from liver while, rising NEFA to be from altered carbohydrate metabolism.

Decreased BCAAs concentration in blood plasma is the most puzzling abnormality in liver disease and thus has been the centre of researches as well. Fischer et al., 1976 hypothesized that low levels of BCAAs decrease production of excitatory neurotransmitters, and high levels of AAAs increase inhibitory neurotransmitters, causing deterioration of cerebral function. Independently from the degree of HE, the concentration of val, leu, ile always is reported to be low in patients (Marchesini et al., 1980). Hyperinsulinemia is suggested to be a probable cause for this condition (Munro et al.) as the entry of neutral amino acids into muscles is regulated by insulin where they are supposed to be metabolized. Along with tis, the relationship with insulin and BCAA plasma levels are regulated by peripheral tissues sensitivity towards the hormone. In type 2 diabetes, BCAA levels increased in plasma despite the high insulin levels in blood (Job et al., 1967). Hayashi et al.,1981 showcased high insulin resistance in liver cirrhotic patients advocating the role of insulin in disturbing amino acids metabolism.

Methionine (M, Met) a mercapto amino acid, toxic to CNS and an etiological factor in HE is released during liver necrosis and is also reported a rise in HE (Tobrek et al., 1995; Higashi 1982).

Hyperinsulinemia cant just be related with hormonal derangement in chronic liver disease, it is reported along with hyperglucagonemia in chronic liver patients (Sherwin et al., 1974) suggesting metabolic disturbances along with. Such condition may be explained a series of events as proposed: enhanced gluconeogenesis, causing a decline in plasma alanine concentration, causing muscles to enhance to enhance its production. Since nitrogen for alanine comes from BCAAs (Schaeffer et al., 1981) thus, a decrease in BCAAs is consequently observed. More details about this hypotheses are found in studies in favour of this, Brodan et al., 1978, Daniel et al.,1977a, spargo et al.,1979. While contradictory results are also presented in a study by Holm et al.,1978 indicating low BCAA in plasma while normal alanine concentration is maintained.

Thus, to conclude the BCAA plasma level reduction in chronic liver disease is likely due to increased uptake of amino acids as a metabolic fuel to muscles and their steady incorporation as muscle protein and fat.

2.2 False Neurotransmitter Hypotheses, The true relation established:

An approach to pathogenesis of chronic liver disease associated neurological disorder is false neurotransmitter hypotheses or also known as weak neurotransmitter hypotheses by Fischer and Baldessarini, 1971. The functioning of all the neurons in CNS are based on neurotransmitters. Electrical signal induction by axons is accompanied by release of post synaptic neurotransmitters including of both excitatory and inhibitory nature. The understanding is based on adrenergic system and neuropharmacology of neurotransmitters. Structurally, peripheral andregenic system and sympathetic nervous system needs hydroxyl-OH group at β position in the chain (Fischer et al., 1965; Kopin, 1968). The central concept of weak/false neurotransmitters is based on the protective role of peripheral andregenic neurotransmitters, to protect from destruction and release substances that are comparatively less active sympathicomimetically than neurotransmitters which then could accumulate in response of toxic conditions (Fischer et al., 1968; crout et al., 1964; Muscholl and Maitre, 1963), similar hypotheses for brain works by the release of aromatic amines as neurotransmitters which as well are less active than putative neurotransmitters (Baldessarini, 1971; Baldessarini and Vogt, 1971), strengthening the hypothesis.

Liver contains portal blood having amines produced by GI tract flora synthesizing amino acids decarboxylases from the contents of gut along with precursor amino acids absorbed into portal circulation. The blood brain barrier (BBB) plays a critical role in controlling neurotransmitter by its selective permeability towards precursor amino acids and disallowing all other circulating amines, this causes the possibility for both peripheral and CNS to be fooled into false or inactive neurotransmitters release, protection and acceptance. Thus, in HE many studies evidenced the accumulation of false neurotransmitters. Because of portosystemic shunt blood is shunted around liver causing a decrease in hepatic function, causing accumulation of abundance of nitrogenous compounds, amino acids or various amines, by escaping liver metabolism, they flood towards central and peripheral nervous system (Fischer and Baldessarini, 1971; Fischer and James, 1972). Norepinephrine depletion in periphery increases cardiac output and causes decreased peripheral vascular clearance, a symptom of hepatic failiure (DelGuercio et al., 1964). Mashford et al.,1962 suggested the relation between low vascular resistance and norepinephrine depletion. With disturbed metabolism of nitrogenous compounds, rise of blood ammonia could be explained as well.

In hepatic coma, a study on rats saw an increase in Octopamine, a false neurotransmitter with potential action less than 1/50 of norepinephrine in periphery. The level elevated in heart and brain (Fischer and Baldessarini, 1971; Fisher, 1974). Similar model and resultant study is seen with another false neurotransmitter Phenylethanolamine as well (Crout at al., 1964).The norepinephrine in comatose dropped to a bizarre level of 50% in comatose patients brain (Dodsworth et al., 1974b).

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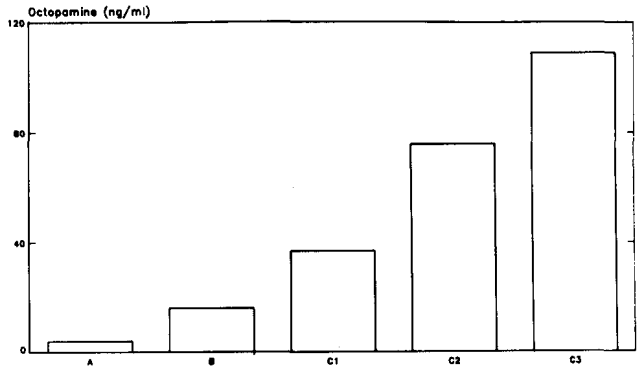

FIG. 1. Plasma octopamine levels in HE and in control subjects. Group A (controls) is formed by 14 cases whose octopamine concentration (M + SE) was 0.40 ± 0.06 ng/ml. Group B (grade 0 HE) by 30 cases with a concentration of 1.56 ± 0.35 ng/ml. Sub-group C1 (grade 1 and 2 HE) by 11 cases with a concentration of 3.69 ± 1.07 ng/ml. Sub-group C2 (grade 3 HE) by 9 cases with a concentration of 7.62 ± 0.92 ng/ml. Sub-group C3 (grade 4 HE) by 6 cases with a concentration of 10.92 ± 4.24 ng/ml. Taken from Rossi-Fanelli *et al.* 1976).

The mile stone unturned in "false neurotransmitter hypotheses" was the observation of norepinephrine depletion in hepatic failure animals which can be explained by having a number of different possible alterations in metabolism (Dodsworth et al., 1974a,b).

While the depletion is being talked about, synthesis of catecholamines a complicated task, and reduced synthesis can find its way back to a competitive inhibition. The synthesis of neurotransmitter depends on plasma concentration (Guroff and Uderfriend, 1962); on brain concentration (Wurtman, 1974) of precursor amino acids, which are involved in a competition with other amino acids to cross BBB (Orlowski et al., 1974).

BCAAs in portacaval anastomosis determine the brain concentration of trp, phe (James et al., 1976). The rise in levels of these amino acids, cause a fall in BCAAs concentration, may facilitate phe to CNS. In brain it inhibits Tyr hydroxylation to dopamine, pioneer step in catecholamine synthesis mediated by tyrosine-hydroxylase. Since, both tyr and phe have similar structure thus, have similar affinity for tyrosine-hydroxylase resulting in competition for binding with tyrosine-hydroxylase enzyme in catecholamine synthesis (Karobath and Baldessarini, 1972). Tyrosine hydroxylase is the rate limiting step and has limited availability, which is exploited by phe and causing tyr formation from it rather than dopamine formation from tyr. Tyr would then undergo decarboxylation to tyramine (David et al., 1974) followed by β hydroxylation by a non-specific enzyme forming dopamine β-oxidase further to octopamine rather than dopamine. trp as well have the ability to inhibit dopamine synthesis by blocking tyr hydroxylation (Wurtman et al., 1974). By such distorted pathways false neurotransmitters get accumulated and competes with dopamine for decarboxylase.

Trp along with its physiological derivative, serotonin have been seen in same hypotheses for HE pathogenesis (Baldessarini and Fischer, 1973). Serotonin as well act as a false neurotransmitter and by accumulation in brain, it displaces endogenous amines establishing the hypotheses. Serotonin has significant impact on consciousness and behaviour, in excess amounts may induce abberant encephalopathic effects. Degradation of trp hold on to liver via formyl-kenurenin pathway (Altman and Gerber, 1967) and because of liver insufficiency in HE, the accumulation of trp in blood and brain happens. Studies have proven rise in trp levels in HE patients (Hirayama, 1971).

3. Amino acid levels in brain and CSF in HE:

Brain dysfunction and liver failure has been studied in synergy from a long time. Liver is an excellent barrier again systemic influx of noxious materials which are either ingested or generated in GI tract. Various potential toxins have established their relation with respect to HE and brain and yet many studies are required to establish their correlation.

A study by James et al., 1976 established HE by portacaval anastomosis in rats and studies the plasma amino patterns in relation with humans, showing a rise in phe, tyr, trp and a fall in ile, val, leu. The results evidenced the fall in these amino acids need to be accompanied with rise in others for competition to cross BBB. Similar results are also translated in other animal models as well (Rossi-Fanelli et al., 1980; Smith et al., 1978). Table 2 by James et al., 1978 compiles the results of studies in rats and the comparison of neutral amino acid concentration in brain and plasma.

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TABLE 2. EFFECT OF PORTACAVAL ANASTOMOSIS ON PLASMA AND BRAIN NEUTRAL AMINO ACIDS

Amino acid	Concentration		
	Control rats	PCA rats	Percentage of control
	Plasma (nmole/ml)		
Valine	242 ± 21	187 ± 11	77.3*
Methionine	60 ± 4	70 ± 4	116.7
Isoleucine	99 ± 7	77 ± 6	77.8*
Leucine	180 ± 17	144 ± 11	80.0
Tyrosine	61 ± 8	120 ± 8	196.7†
Phenylalanine	69 ± 4	119 ± 8	172.5†
Histidine	67 ± 5	107 ± 5	159.7†
	Brain (nmole/g)		
Valine	95 ± 6	92 ± 7	96.8
Methionine	51 ± 5	84 ± 3	164.7†
Isoleucine	39 ± 1	37 ± 2	94.9
Leucine	79 ± 3	91 ± 5	115.2
Tyrosine	53 ± 5	185 ± 8	349.1†
Pheylalanine	47 ± 2	151 ± 8	321.3†
Histidine	58 ± 3	166 ± 6	286.2†

Groups of 8 control rats and 11 rats with a PCA were anesthetized with phenobarbital and 10 min later were decapitated. Data are presented as mean ± standard error (S.E.) and were analyzed by Student's *t*-test. The last column shows the concentration of each amino acid in the PCA rats as a percentage of that in the control rats.

* $P < 0.05$ compared to control values.

‡ $P < 0.001$ compared to control values.

Taken from James *et al.* (1978).

These findings strongly favour the close relationship between CSF amino acid accumulation of tyr, phe, trp, glu, met. The accumulation of these amino acids in directly related to severity and degree of HE. Rossi-Fanelli et al., 1982a showcased this in dogs by rising brain levels of aromatic amino acids and called it "brain-toxicity". The best results obtained with adding 1% phe + 1% trp or 1.5% phe + 0.5% trp to render animals as comatose.

Octopamine, a well-established false neurotransmitter involvement in neurological depression was reported by Chance et al., 1985. By giving I.V. octopamine injection to rats. Regardless of their liver condition, neurological depression was established, further addition of trp worsened it.

The investigations and experiments can be concluded to establish the relation in rise of false neurotransmitters precursor amino acids (phe, tyr, trp) in CSF and HE like neurological symptoms. The role of BBB is as well involved in HE pathogenesis via amino acids.

4. Treatment of HE by amino acids:

   Amino acid are widely used in treatment of HE and liver cirrhosis widely. The above stated hypotheses "false neurotransmitter hypotheses" indicates the beneficial role of amino acid pattern in HE and liver patients by reducing the influx of AAAs in brain. Fischer et al., 1976 proposed the administration of amino acid mixtures enriched in BCAA for liver patients. The composition is managed in a way to contain BCAA and

small amounts of AAA along with met to adjust adequate nitrogen supply to reverse HE. The beneficial impacts are well studied in both controlled and uncontrolled trials by Fischer et al., 1976; Fiaccadori et al., 1984. The studies are performed exclusively with BCAAs as well (Capocaccia et al., 1979) in severe HE patients. The results showcase the beneficial effects of BCAA administration in HE.

BCAA serves as energy source, up to 30% energy requirements are fulfilled in HE patients, in decomposed liver cirrhosis patients with fewer glycogen store, ketogenesis and fatty acid utilization is reduced. Sherwin, 1978 suggested the leu administration to increase protein synthesis and decreased muscle breakdown. The BCAA administration to patients with chronic liver failure, normalization of amino acid pattern in plasma probably due to reduced proteolysis or increased utilization of AAA for protein synthesis (Rossi-Fanelli et al., 1981). In such patients, reduced ammonia level in plasma is also observed because of its increased metabolism in skeletal muscle.

4.1 BCAA as a treatment:

Several studies utilized BCAA in combination with varying percentages or exclusively BCAA to check on its therapeutic effects in HE patients (Fischer et al., 1976; okada et al., 1981; Capocaccia et al., 1979). With positive clinical results, several complications like protein intolerance is as well observed. The administration of BCAAs along with an energy source like dextrose to HE patients, indicated positive outcomes (Rossi-Fanelli et al., 1981; Fiaccdori et al., 1984) are are strongly suggested. Rossi-Fanelli et al., 1982b as well demonstrated improvement in mental condition and a revert to normal amino acid levels from altered state by BCAA administration. Though, the return was transitory and returned back to altered values as reported during HE, with alert patient state. The alert state thus evidenced the role of BCAA in close coordination with brain and mental state of patients. The behaviour of both plasma ammonia and CSF glu was similar with significant reduction during BCAA administration and did not quite rise afterwards as well.

5. Summary, Conclusion and Future perspectives:

The consideration of etiology, patho-physiology of HE has undergone a radical shift with strenuous researches. The metabolic derangements in HE, with liver failure must as well be considered with it. The biochemical mechanisms in HE needs to be considered step by step with critical evaluation of each step though is complex but a consequential mosaic of events in which HE and amino acids are tightly linked.

The found corner stones in experimental studies to improve future knowledge are:

a. Significant alterations in CNS, neurotransmission is responsible in characterizing HE and other symptoms in it.
b. Amino acid imbalance in plasma levels shows 'condicio sine qua non' in He.
c. Impairment in BBB and functional transport of amino acids along it plays crucial role in synaptic neurotransmission alterations, developing HE symptoms
d. Tailored amino acid mixtures can be used for reduction of brain entry of toxic amino acids.

The tailored approach, more experimental and clinical study seems to be future awakening for HE, for future researches the emphasis on energy metabolism, on pathogenic mechanism of HE must be kept in light.

References:

1. 1, f51-54. delguerc1o,l. R. M:, commaraswarry,r. P., feins, n. R. Et al. (1964) pulmonary arterio-venous admixture and hyper dynamic cardio vascular state in surgery for portal hypertension.surgery 56, 57--74. 273-304.
2. Altman,k. I. And gerberg, . B. (1967)catabolism of tryptophan by the isolated, perfused liver andintestine. Nature 213, 9ll-913.
3. Baldessarini, r. J. And vogt,m. (197i) the uptake and subcellular distribution of aromatic amines in the brain of the rat. J. Neurochem.18, 2519-2533.
4. Baldessarini,r. J. (1971) releaseof aromatic amines from the brain tissues of the rat in vitro. J. Neurochem. 18, 2509-2518.
5. Baldessarinir, .j.and karobatn,m. (1973)biochemical physiology of central synapses .a. Rev.physiol.35,
6. Baltessarini,r. J. (1972)biogenic amines and behavior. A. Rev. Med. 23, 343-354. Baliessamni,r.j.andfischerj,.e.(1973)serotonin metabolism in rat brain after surgical diversion of the portal venous circulation. Nature (new biol.) 245, 25-27.
7. Capocacciat, calcaterrav, cangianoc,.etal.(1979) therapeutic effects of branched-chaianminoacids in hepatic encephalopathy a preliminary study. In: medical and surgical problems of portal hypertension, pp 239-249.
8. Cardelli cangianop., cangiano,c., jamesj,.h., jeppssonb,. ,brennerw. And fischerj,.e.(1981) uptake of amino acids by brain microvessels isolated from rats after portacavalanastomosis j.. Neurochem.36(2), 627~32.
9. Cardelli-cangiano,p., cangiano,c., james,h.j., ceci,f., fischerj,.e.and strom,r.(1984)effect of ammonia on amino acid uptake by brain micro vessels. Biol.chem.259,5295-5300.
10. Christensen,h. N. (1969) some special kenetic problems of transport.adv. Emymol. 321, 1-20.
11. Christensen,h. N. (1973) on the development of amino acid transport systems.fedn proc. 32, 19-28.

12. Christensen,h. N. (1979) developments in amino acid transport, illustrated for the blood-brain barrier. Biochem. Pharmac. 28, 1989-1992. cohen,r. A., kop1n,i. J., creveling,c. R., musacchio,j. M., fischerj. E.. Crout,j. R. And gill, j. R. Jr. (1966) false neurochemicaltransmitters.ann. Intern. Med. 65, 347-362.
13. Daniel, p. M., pratt,o. E. And wilson,p. A. (1977b)the influx of isoteucineinto the cerebral hemispheres and cerebellum: carrier-mediated transportand diffusion. Q. Jl exp. Physiol. 62, 163 173.
14. Daniel, p. M., pratt,o. E. And wilson,p. A. (1977c) the exclusion of l-isoleucine or of l-leucine from the brain of the rat, caused by raised levelsof l-valine in the circulation, and the mannerin which this exclusion can be partially overcome.j. Neurol. Sci. 31, 421~431.
15. Daniel, p. M., pratt,o. E., and wilson,p. A. (1977d)the transport of l-leucine into the brain of the rat in vivo: saturable and non-saturable components of influx. Proc. R. Soc. Lond. B. 196, 333-346.
16. David,j.c.,dairman,j.c.andudenfriend,s.(1974)decarboxylation to tyramine: a major route of tyrosine metabolism in mammals.proc. Nard. Acad. Sci. U.s.a. 71, 1771-1777.
17. Deboer,j.e.g.,oosterbroekr,.j.,janssen,m. A., wesdorp,r.i. c.andsoetersp,.b.(1982)fate of leucine in muscle and adipose tissue in male sprague-dawley rats with portacavalshunts(pcs).clin. Nutr.
18. Dodsworth,j. M., cummings,m. G., james,j. H. And fischer,j. E. (1974a)decreased brain norepinephrine in actue hepatic coma. Gastroenterol. 66, 881-884. dodswortrl, j. M., james, j. H., cummings, m. G. And fischer, j. E. (1974b) depletion of brain norepinephrine in acute hepatic coma. Surgery 75, 811 820.
19. Dodsworth,j. M., james,j. H., cummings,m. G. And fischer,j. E. (1973) diagnosis and therapy of hepatorenalsyndrome: a tentative classification.surg. Forum. 24, 396-398.
20. E. (1972) neurotransmitters and hepatic failure. Conn. Med. 36, 575-581. e., (1974) false neurotransmittersand hepatic coma. Res. Pubis ass. Res. Defy. Ment. Dis. 53,
21. E. And baldessarini,j. R. (1971) false neuro transmitters and hepatic failure. Lancet ii, 75-79.
22. E., and james,j. H. (1972) treatment of hepatic coma and hepato renal syndrome: mechanisms of action of l-dopa in hepatic coma. Am. J. Surg. 123, 222 230.
23. Eds. L. Capocaccia, j. E. Fischerand f. Rossi-fanelli.plenum: new york. Samuels,s. And fish, i. (1978) procedurefor measuremenot f amino acid transport from blood to brain in small animals. Analyt. Biochem. 87, 447-454.
24. Eds. L. Capocaccia,j. E. Fischerand f. Rossi-fanelli.plenumpress: new york. Fischer,j. Fischer,j. 53-73. Fischer,j. Fischer,j.
25. Eds. M. J. Orloef,s. Stipaand v. Z1paroacademicpress:london. Capocaccia,l., cangiano,c., attili, a. F., angelico,m., cascino,a. And rossi-fanellif, . (1977) octopamine and ammonia plasma levels in hepatic encephalopthy.clinica chim. Acta 75, 99-105.

26. Fiaccadori,f., ghinelli, f., pedretti,g., pelosi,g., sacchini,d. And spad1ni,g. (1981) negativenitrogen balance in cirrhotics. Ric. Clin. Lab. 11, 259 270. fiaccadori,f., ghinelli, f., pedretti,g. Et al. (1984) branched-chain amino acid enriched solutions in
27. Fischer,j. E., horst,w. D. And kopin, i. J. (1965) fl-hydroxylated sympatho mimeticaminesas false neurotransmitters.br. J. Pharmac. 24, 477~484.
28. Fischer,j. E., wiese,v. K. And kopin, 1. J. (1968) false adrenergic transmitter release from the isolated cat heart. Am. J. Med. Sci. 225, 158-162.
29. Fischer,j. E., yoshimura,n., aguirre,a., james,j. H., cummings,m. G., abel, r. M. Deindoerfer, f. (1974) plasma amino acids in patients with hepatic encephalopathy.am. J. Surg. 127, 40-47.
30. Fischer,j.e.,rosen,h.m.,ebeid,a.m.,james,j.h.,keane,j.m.andsoetersp,.b.(1976)the effect of normalization of plasma amino acids on hepatic encephalopathyin man. Surgery 80, 77-91.
31. Freund,h., dienstag,j., lehrich,f., yoshimura,n., bradford,r., rosen,h., atam1an,s., slemmer, e., holroyle, j. And fischer,j. E. (1982) infusion of bacc solution in patients with hepatic encephalopathy.ann. Surg. 196, 209-213.
32. Ross1-fanelli,f., freund,h., krause,r., smith,a. R., james,j. H., castorina-ztparo,s. And fischer, j. E. (1982a)induction of coma in normal dogs by the infusion of aromatic aminoacids and its prevention by the addition of branched-chainamino acids. Gastroenterology83, 664-671.
33. Rossi-fanelli,f., cangiano,c., attili, a., angelico,m., cascino,a., capocaccia,l., strom,r. And crifo,c. (1976). Octopamine plasma levels and hepatic encephalopathy a: re-appraisal of the problem. Clin. Chim.acta, 67, 255-261.
34. Rossi-fanelli,f., cangiano,c., cascino,a., merli, m., riggio,o., stortoni,m. And capocaccia,l. (1984) branched-chainamino acids in the treatment of severe hepatic encephalopathy.in: hepatic encephalopathy in chronic liver failure, pp. 335 344.
35. Rossi-fanelli,f., escourrouj,., smith,a. R. And fischer,j. E. (1980) phenyl ethanol amina end octopamine in hepatic encephalopathy.in: non catecholic phenylethylamines,pp. 231 244. Eds. A. D. Mosnaimand m. E. Wolf. Marcel dekker inc: new york.
36. Rossi-fanelli,f., riggio,o., cangiano, c. Et al. (1982b) branched-chainamino acids vs. Lactose in the treatment of hepatic coma: a controlled study. Dig. Dis. Sci. 27, 929-934.
37. Rossi-fanellif., angelic, m., cangiano,c., cascino,a., capocaccia,r., de concilis,d., riggio,o. And capocaccia,l. (1981)effect of glucose and/or branched-chainamino acid infusion on plasma amino acid imbalance in chronic liver failure. J. Ent. Parent. Nutr. 5, 414~19.
38. Schaefferm, . C., rogersq, . R., wolfe,b. M. And lecouteur,r. A. (1981) effects of glutaminefeeding on plasmaandcerebrospinalfluid ammoniain potacavalshuntdogs. 12thint. Congr.nutr., sandiego, abstract book. 840.
39. The treatment of hepatic encephalopathy a: controlled trial. In: hepatic encephalopathy in chronic liver failure, pp. 323-334.