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Gut Uptake, Brain and Behaviour

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TDB and KLR designed the study and wrote the first draft of the manuscript. Authors KLR and TDB managed literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: To document the evidence for a gut uptake to brain axis. The many hormones, many of them peptides and shared by the intestines and the brain, will not be included in this survey.
Methods: Systematic looking through journal publications by means of Pub med and collected information and authors research since 1978.
Results: Food-protein antibodies, food-protein derived peptides and direct physiological evidence point to considerable effect of the digestive system on behavior and mood. Removal of specific proteins from diet ameliorates the clinical condition.
Conclusion: Uptake from the gut of various substances has effect on behaviour.

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1. INTRODUCTION

What is taken up from the gut can have profound effects on behaviour. Thus most of us know the effect of alcohol which changes the timid to the brave, the extreme extrovert to a raving fool etc. The small concentration of ethanol necessary for these effects is in the range of a few parts per thousand by volume. Moreover dietary deficiencies also have profound effects on development and behaviour.

In this paper disorders of carbohydrate uptake is followed by data on increased protein uptake, and then increased peptide levels in urine.

Furthermore we present physiological and epidemiological studies on a gut to brain connection, and finally effects of removing the proteins that have caused antibody increase and peptide increase.

2. DECREASED UPTAKE FROM THE GUT

Lack of vitamins can cause disorders like rickets in the case of Vitamin D, scurvy in the case of Vitamin C, and both show mental effects. Lack of thiamine (B1) caused a schizophrenia-like psychosis among poor persons with mainly Maize as their source of food and Korsakoff psychosis in alcoholics. In the southern states of USA many were cured of their psychosis when treated with thiamine. A similar story pertains to Niacin. Hydrops and Kwashiorkor in the case of too little protein is also well known. All these states also have psychological effects.

Deficient availability of tryptophan to the brain may cause dementia in some apparently Alzheimer like states [1]. Lack of tryptophan may also be caused by competition for the uptake of this amino acid with DOPA used as treatment for Parkinson's disease. Carcinoid tumors in the gut that uses all available tryptophan locally can cause severe dementia [1].

3. INCREASED UPTAKE OF METABOLITES AND POSSIBLE CONSEQUENCES

For an average adult the gut total surface is close the soccer field in size due to the many crypts and projecting villi into the gut lumen. Therefore even small increases in the normal uptake can become considerable due to this large surface area. Normal uptake combined with decreased breakdown also causes serious accumulation of metabolites as seen in Phenylketonuria, where Phenylalanine is not sufficiently metabolized. Removing phenylalanine from the diet prevents serious mental retardation.

4. DISORDERS OF CARBOHYDRATE UPTAKE

Many natural sugars are disaccharides such as Lactose (Glucose and Galactose), Sucrose (Glucose and Fructose).

In many Asian and African persons lactase, the enzyme that breaks down Lactose (milk sugar), is insufficient after the age of about 6. In adopted children to the western countries with high dairy consumption, this frequently causes problems of attention, restless traits, abdominal pain and sometimes aggression [2]. It seems that the disaccharides are taken up

into enterocytes and these become hyper-osmotic followed by increased water uptake and change of shape that cause the para-cellular pathways to open [2]. This state causes uptake of gut content and often inflammatory changes of the gut lining. This pertains also to other disaccharides in a similar fashion.

A feature of highly refined carbohydrate intake is that it causes a rapid rise in blood Glucose followed by fast secretion of insulin to facilitate cellular uptake of the carbohydrates [3]. This is followed by a rapid decrease and in some persons a transient hypoglycemia after about 1/2 to 1 hour. Also serotonin levels are then decreased. Low serotonin and hypoglycemia may cause aggression, inattention and lead to driver accidents [4]. High fiber intake tends to counteract these events.

5. PROTEIN UPTAKE

In normal persons proteins are taken up from the gut [5,6] and this has been shown for casein, lacto-globulin, gliadin and glutenin. Even if just a little is taken up per square cm of gut mucosa, these proteins can be identified and measured in mother's milk [7-10]. Opening an even larger perspective in pathology is the fact that intact eaten enzymes can be found in blood or serum [11,12]. Thus peroxidase and carboxy-peptidase and other enzymes have all been recovered from serum. Botulinum toxin is a proteinase or peptidase derived from Clostridia and is taken up from the gut, passes the blood-brain "barrier", enters the pre-synaptic body, and splits the SNAP- 25 protein at one peptide bond. This effect may kill you [13]. It used to be a problem with home preserved foods. Tetanus toxin has a similar pathophysiology.

These data show that a whole new avenue of approach in pathology can be envisioned, where uptake of intact enzymes especially after "leaks" in the gut mucosa, can cause unexpected results. Zonulin thus reacts with gliadin and bacterial products to open tight junctions in the intestinal mucosa [14] and therefore increases the permeability of the gut mucosa.

Increased uptake of proteins usually cause increased antibody formation and this has been shown in several disorders (Table 1). If antibodies are bound as complexes with antigen these may also be found in patients [38]. Complement-antigen-antibody complexes may further more be recovered from the mucosa or submucosa (see Torrente et al. Table 4). Fragments of proteins (peptides) can, by binding as epitopes to macromolecules, also induce antibodies.

Antibodies against gliadin caused degeneration of the large Purkinje cells in the cerebellum often with peripheral polyneuritis [35], which illustrates the possible consequences of increased and intact protein uptake. Taken up proteins may be active either directly or indirectly as antibody inducing compounds. Antibodies towards food proteins taken up from the digestive tract can also cross react with endogenous cell surface proteins such as enzymes, which can thus be inhibited. This may be considered a kind of autoimmune state. Through such a mechanism, enzymes like angiotensin II converting enzyme is inhibited with physiological and behavioural consequences [43].

In autism casein and gliadin may release inflammatory cytokines [44], and such cytokines increase permeability of epithelial "barriers" [45]. There is considerable evidence that Aluminum (Al) can also increase trans-epithelial transport both from the gut and into the brain [46]. This may be important since Al used in various adjuvant preparations during

immunization may stay in the tissues for a very long time [47] with biological effects. We thus have evidence of a functional Al increase in Alzheimer [48]. Injected Al used as adjuvant in cooperation with mercury (Hg) have been found increased in autism [49], where the gut permeability is increased [50]. In autism opioid peptides of the exorphins type are also increased (Table 2).

Table 1. Food antibodies in different disorders

Disorder	References
Autism spectrum	Reichelt et al. [15]; Lucarelli et al. [16]; Cade et al. [17]; Vojdani et al. [18]; Kawashti et al. [19]; Trajkowski et al. [20]; Lau et al. [21]; deMagistriset al.[22]
Depression	Sælid et al.[23]; Maes [24]
Bipolar	Severance et al. [25]
Rett	Reichelt & Skjeldal [26]
Multiple sclerosis	Reichelt & Jensen [27]; Shor et al. [28]
Celiacdisease	Many references. Eg. Sollid [29]
Down syndrome	Kanavin et al. [30]; Reichelt et al. [31]; Failla et al. [32]; Carlsson et al. [33]; Nygaard et al. [34]
Gluten ataxia	Hadjivassiliou et al. [35]
Schizophrenia	Dohan et al. [36]; Reichelt & Landmark [37]; Samaro et al. [38]; Dickerson et al. [39]; Severance et al. [40]; Jin et al. [41]; Niebuhr et al. [42]

Legend to Table 1: Reference no in parenthesis is found in the reference list. The antibodies are of the IgA and IgG type and not IgE often found in allergic pathology

Table 2. Disorders with increased peptide levels in the first morning urine

Syndrome	References	Remarks
Autism spectrum	Reichelt et al. [15]; Cade et al. [17]; Shattock et al. [59]; Shanahan et al. [60]; Remme et al. [61]; Reichelt et al. [62]; Kost et al. [58]	Tveiten et al. used fragmentationmassspectroscopy (MS/MS)
Schizophrenia	Hole et al. [54]; Drysdale et al. [63]; Idet et al. [64]; Lindström et al. [65]; Cade et al. [17]; Tveiten and Reichelt [66]	Tveiten and Reichelt studied schizoaffective patients and used MS/MS
Depression	Ågren et al. [67]; Sælid et al. [22]; Liu et al. [68]	In mania usually lower than controls
AD/HD	Reichelt et al. [69]	
Multiple sclerosis	Jensen et al. [70]	In “Schub” (worsening)
Alzheimer	Nataf et al. [49]	
Celiac syndrome	Reichelt et al. [71]	Normalizedafter diet
Down syndrome	Nygaard et al. [72]	
Anorexianervosa	Hellzen et al. [73]	
Rett	Solaas et al. [74]	

Legend to Table 2: Many of the peptides need analysis with mass spectroscopy and MS/MS (fragmentation mass-spectroscopy)

6. UPTAKE OF PEPTIDES

Peptide uptake from the gut is well documented [51] and in cases where the breakdown of peptides is inhibited or lacking, the peptide uptake is increased [52,53]. Since many peptides are active in the pico- and nano-molar range, this may have considerable consequences. Thus exorphins like bovine β casomorphin 1-7(YPFPGPI) have been shown to cause analgesia, hyperactivity and later catatonia [54,55]. Casomorphins also cause abrogation of separation distress calls in newborns and social indifference in several species [56]. All these changes were blocked or reversed by opium antagonists. Also in vivo by means of the Ungerstedt model in rats, where the substantia nigra was uni-laterally destroyed with 6-OHdopamine, an opioid induced dopamine increased activity due to decreased dopamine uptake into the synapse, was demonstrated [54]. Cade's group in Florida injected casomorphin 1-7 IV and could show immune reactive FOS antigen increase in key nuclei of the brain in rats [57]. Thus N. accumbens, which is electro-physiologically changed in schizophrenia, showed a remarkable increase. Both of the sensory relay stations such as the colliculus medialis and lateralis and also the visual cortex showed this effect. In human infants there is an inverse correlation of casomorphin1-7 (bovine) to the development of children with psychomotor problems [58].

In autism and schizophrenia exorphins have been determined with MS/MS, and the fragmentation pattern is identical to synthetic standards [62,66]. Mass spectrometry and MS/MS is the modern gold standard of peptide technology.

7. UPTAKE OF PEPTIDES AND PROTEINS THROUGH THE BLOOD BRAIN BARRIER

Casomorphins are taken up as other opioids are [75-78]. The prions are probably Proteins and induce Kuru [79]. The fact that IgG immune-globulins can act on nerve cells in the brain [35] indicates that this barrier is not absolute for either proteins or peptides. One of the most symptom rich psychoses known is post–partum psychosis, where human casomorphine immune-reactive peptides are increased in serum and CSF, and may be the mediators of this disorder [80], even if formed in the breasts.

8. PHYSIOLOGICAL EVIDENCE FOR A GUT –BRAIN AXIS

Persons with inflammatory bowel disease given an ordinary breakfast showed numerous peri-vascular hive-like reactions in the white substance of the brain studied with NMR [81-82]. Furthermore children on a gluten free diet for one year because of coeliac disease, who underwent provocation with gluten, demonstrated EEG changes [83]. Some of these children retained these EEG changes for months. Egger's group demonstrated that AD/HD children showed magnetic EEG changes after provocation with food to which they reacted found by means of an elimination diet [84,85]. In celiac disease cerebral calcifications and epilepsy were found as a special syndrome [86].

9. EPIDEMIOLOGICAL EVIDENCE

A series of epidemiological studies have shown that gastrointestinal problems predispose for psychiatric symptoms and traits (Table 3). Up to more than 70% of these patients run into psychiatric problems. Asperger also described autistic traits in celiac children [87]. Since this

relationship is found in different countries these data carry a lot of weight (Table 3). The number of subjects recorded was very large.

Table 3. Epidemiology

No.	References	Country
1	Dohan [88]	Papua and pacific islands
2	Hallert et al. [89]	Sweden
3	Lydiard et al. [90]	USA
4	Addolorato et al. [91]	Italy
5	Gupta et al. [92]	USA
6	Alanderet al. [93]	Sweden
7	Haug et al. [94]	Norway
8	Ludvigsen et al. [95]	Sweden
9	Pynnönen et al. [96]	Suomi-Finland
10	Kunna et al. [97]	England

Legend to Table 3: Reference no in parentheses. In this Table the listed numbers 3-7 show that up to more than 70% with gastrointestinal problems acquire psychiatric symptoms of varying severity and types. Pynnönen et al. [96] dealt with psychiatric deviations in celiac disease

Several reports of gastrointestinal signs of inflammation and/or chronic inflammatory states exist in autism and schizophrenia. Some are listed in (Table 4).

Table 4. Anatomical evidence for gut changes of inflammatory nature in schizophrenia and autism

Disorder	References	Comment
Autism	Horvath [98]; Wakefield et al. [99]; Torrente et al. [100]; Krigsman [101]	Inflammatorymucosalchanges
Schizophrenia	Reiter [102]; Buscaino [103]; Hemmings [104]; Severance et al. [105]	Signs of chronic gut inflammation
IBD chronic	Welch et al. [106]	Matching brain areas abnormal in autism

Legend to Table 4: IBD is Inflammatory Bowel Disease. Numbers in parentheses refer to the literature list

A reasonable approach to some of these disorders would be to remove the antibody inducing proteins and precursors of the probable involved peptides. If sufficient vitamin and trace mineral supply is assured, as well as calcium, no serious side effects have so far been registered. (Table 5) gives an overview of effect of gluten-and casein-free (gf/cf) diet in several disorders. What is generally known as a ketogenic diet is largely a reduction in bread (gluten) intake, and is often tried in some neurological syndromes.

10. FACTORS THAT INCREASE GUT PERMEABILITY

First and foremost are inflammations of the mucosa, both bacterial and viral. Clostridia and gliadin can act through Zonulin and open the tight junctions [14]. Furthermore di- and poly-saccharides that are not broken down, can open the para-cellular pathways [2]. Casein and gliadin can release inflammatory cytokines in the intestinal mucosa as shown in autism [44].

Absent or decreased activity of specific peptidases increases the uptake of peptides [51,52]. Also Al and Hg do change the permeability of the gut as well as the blood-brain barrier. As would be expected, peptidase defects or inhibition increase urine excretion of peptides [120-122]. Finally the intestinal mucosa is exceptionally sensitive to high energy radiation.

Table 5. Dietary intervention are reported, mostly gluten and casein free diet (gf/cf), in various disorders

Disorder	References	Comment
Autism spectrum	Reichelt et al. [15]; Lucarelli et al. [16]; Cade et al. [17]; Knivsberg et al. [107]; Knivsberg et al. [108]; Pennesi et al. [109]	Open studies of more than12 weeks
Autsmspectrum	Knivsberg et al. [110]; Whiteleyet al. [111]	Single blind randomlyassigned
AD/HD	Egger et al. [112]; Pelsser et al. [113]	Randomlyassigned and controlled
AD/HD	Boris and Mandel [114]; Reichelt et al. [69]	Open study more than 1 year diet
Schizophrenia	Dohan et al. [115]; Singh and Kay [116]; Reichelt et al. [117]; Cade et al. [17]	Observed over more than a few weeks.
Down	Reading [118]	
Celiac	Pynnönen et al. [119]	Especially the psychiatric symptoms

Legend to Table 5: Only papers of sufficient experimental length of time are included (more than 3 months). Numbers in parenthesis refer to the reference list

11. CONCLUSION

Rather overwhelming evidence is now available that gut uptake can modify brain function. This may act both ways, but in this review the gut to brain inputs have been singled out for study. Many of the peptides still need analysis with mass spectroscopy and MS/MS (fragmentation mass spectroscopy), hydrolysis and amino acid analysis.

However, auxiliary data confirm the importance of casein and gliadin to behaviour. An excellent overview of the discussed problem is that of Wakefield et al. [123], and also the case argued for schizophrenia [124] and Autism [125].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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