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Chapter 7

Nonpharmacological Inhibition of Cerebral Dopaminergic Activity May Be an Option for Medication-Resistant Hallucinations

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Abstract

Some percentage of patients experience hallucinations that are not responsive to different classes of neuroleptic drugs and to electroconvulsive therapy. Interestingly, some nonpharmacological treatments can inhibit dopaminergic activity in the brain and produce physiological effects that are similar to those of neuroleptic medication, suggesting that these approaches may potentially be useful as a therapeutic option for medication-resistant hallucinations. Two examples are temporary hyperthermia and low-protein diets.

A temporary increase in core body temperature via external heating, such as immersion in hot water (39-40 degrees Celsius), can increase the plasma and brain level of serotonin and the plasma level of prolactin. Hyperthermia typically induces fatigue and can cause lethargy and loss of motivation. All of these changes are consistent with increased serotonergic and reduced dopaminergic activity in the brain. It is also noteworthy that cerebral serotonergic neurons, for the most part, have inhibitory projections to dopaminergic neurons.

Low-protein diets lower the plasma levels of tyrosine and phenylalanine, which are metabolic precursors of cerebral dopamine. Experiments on laboratory rats have shown that low-protein diets can lower the total concentration of dopamine in the striatum and reduce the density of dopamine D2 receptors in this brain region. Low protein diets are also known to impair the coping ability of laboratory animals in experimental models of depression such as Porsolt swim test. These changes are consistent with reduced dopaminergic activity in the brain and are similar to the effects of neuroleptic drugs. It should be noted that neuroleptics inhibit most dopamine receptors and tend to reduce

dopaminergic transmission overall, although these drugs typically cause a compensatory increase in the density of D2 receptors and a temporary increase in the level of extracellular dopamine due to inhibition of presynaptic D2 receptors.

The two aforementioned treatments cannot be used on a permanent basis, but each of them can be used intermittently, for example, 30-minutes of whole-body hyperthermia per day or alternation of one week of very-low-protein diet with two weeks of a balanced diet. Although the proposed treatments are temporary, they may produce lasting changes in the dopaminergic system due to neural plasticity. Clinical effectiveness of these approaches is currently unknown. The dietary approach is likely to be safe to use in combination with pharmacotherapy, whereas hyperthermic treatments are known to be dangerous for patients taking neuroleptics.

Introduction

Hallucinations, particularly auditory hallucinations (the person is "hearing voices," often unpleasant and derogatory voices), are among the most typical symptoms of a psychotic episode as defined in the Diagnostic and Statistical Manual of Mental Disorders [1]. Hallucinations can also occur during a manic episode [1] and in some organic brain disorders such as Parkinson's disease [2]. In the context of the diagnosis of schizophrenia, hallucinations belong to the category of "positive symptoms," as do bizarre delusions and disorganization of thought/speech [3]. The adjective "positive" here means that these symptoms "add something new," so to speak, to the symptomatology of a patient, while the so-called "negative symptoms," namely, emotional blunting, social withdrawal, poverty of thought, and demotivation, "subtract," as it were, from existing personal qualities of a patient. Aside from the positive and negative symptoms, there is another category, namely, "cognitive symptoms" of schizophrenia, which include deficits in attention and short-term memory. Patients diagnosed with schizophrenia do not always experience hallucinations; however, the existing biological theories of hallucinations overlap to a large extent with the existing theories of schizophrenia [4]. Etiology of schizophrenia is believed to involve an unknown combination of genetic and environmental factors [5]. Several factors of small effect may collectively contribute to the development of the illness, while no single factor has a strong causal association with schizophrenia [5]. Particularly, no single gene has been shown to cause schizophrenia so far, while large groups of genes may be associated more strongly with this disorder [6]. It is noteworthy that brain imaging studies found some abnormalities in the brain structure of schizophrenic patients, but these deviations are relatively small, on average, and fall within the normal range [5]. Therefore, brain imaging, genetic analyses, and other laboratory tests cannot be used to diagnose schizophrenia at the time of this writing and this disorder is currently diagnosed using a special questionnaire and a clinical interview.

Hallucinations can also be caused by detectable physical changes in the brain, such as those that occur during Parkinson's disease, Alzheimer's or other neurodegenerative diseases. The former disorder is characterized by a progressive loss of dopaminergic neurons that project to the striatum and some patients with Parkinson's present with hallucinations [2].

Several theories regarding pathophysiology of hallucinations have been proposed in the last half century [4]. The "dopamine hypothesis of psychosis" is one of the few theories that have been widely applied to the development of therapeutic agents during that past two decades. This theory derives from a serendipitous finding that drugs which block dopamine

D2 receptors can reduce hallucinations and other psychotic symptoms in schizophrenic patients [7]. Conversely, drugs that increase extracellular level of dopamine in the brain such as cocaine and amphetamine, when administered at high doses, can cause positive symptoms of schizophrenia (e.g. delusions and hallucinations) in healthy people [8]. According to the dopamine hypothesis, schizophrenia may be associated with increased sensitivity of dopamine D2 receptors in the striatum [8]. Therefore, pharmacological antagonists of D2 receptors would be expected to reduce psychotic symptoms. Traditional antipsychotic drugs such as haloperidol and chlorpromazine are believed to exert their action through this mechanism and these pharmacological agents can significantly reduce positive symptoms (including hallucinations) in up to 60% of schizophrenic patients without causing significant sedation [5,9]. Serious concerns have been raised about the side effects of chronic administration of the traditional antipsychotics, which may include motor abnormalities such as akathisia, bradykinesia, tremor, tardive dyskenisia and muscle rigidity (so-called extrapyramidal symptoms) as well as neuroleptic malignant syndrome (hyperthermia, delirium, unstable vital signs, rigidity) [9]. The motor side effects are thought to result from the blockade of dopamine D2 receptors in the basal ganglia (located in the dorsal striatum) which are involved in the regulation of the motor function. The peculiarity of extrapyramidal symptoms is that they often persist even after withdrawal from antipsychotic drugs [9].

The dopamine theory of psychosis was updated in the last two decades in order to explain the role of serotonin 5-HT2A receptors in the pathophysiology of psychosis as well as the clinical effectiveness of the newer generation of “atypical” antipsychotics, which have a relatively low affinity for dopamine D2 receptors and a stronger inhibitory effect on 5-HT2A receptors [8,9]. It was found some time ago that many hallucinogens (e.g., mescaline and lysergic acid diethylamide) stimulate serotonin 5-HT2A receptors in the brain, and their psychotogenic effects can be blocked by 5-HT2A antagonists [10]. Unfortunately, selective 5-HT2A antagonists do not reduce hallucinations in schizophrenia and neurodegenerative disorders and it is currently believed that clinically effective antipsychotic drugs must have a significant inhibitory effect on 5-HT2A receptors and at the same time exert a moderate-to-weak inhibitory effect on dopamine D2 receptors [5,10]. This sort of antipsychotic agents, which exert dual action by inhibiting dopamine D2 and serotonin 5-HT2A receptors, are expected to cause a lower incidence of dopamine-related side effects compared to the typical antipsychotics such as haloperidol. The atypical antipsychotic drugs such as clozapine, olanzapine and risperidone, which fit the above pharmacodynamic criteria, indeed have a significantly lower risk of extrapyramidal symptoms at clinically effective doses [5,9].

Clozapine seems to stand out among other atypical antipsychotics with respect to its high clinical effectiveness: a high percentage of patients who do not respond to either traditional or atypical antipsychotics seem to benefit from clozapine and the mechanism of this effect is unknown [5,9]. Additionally, clozapine can improve negative symptoms in some patients, while most neuroleptics (both traditional and atypical) have little or no effect on negative symptoms of schizophrenia [5]. At present, clozapine is the only proven treatment for hallucinations in patients with Parkinson’s disease [11]. Incidentally, the affinity of clozapine for dopamine D2 receptors is approximately 10-fold lower than that of haloperidol and clozapine’s occupancy of striatal D2 receptors is some 2 to 3 times lower than that of haloperidol at clinically effective doses [10,12]. It has been hypothesized that the anomalous effectiveness of clozapine may have to do with its simultaneous inhibition of a broad range of dopaminergic (D1, D2, D3, D4), serotonergic (5-HT2A, 5-HT2C, possibly 5-HT3 and 5-HT6,

plus partial agonism of 5-HT1A) receptors plus its interaction with some adrenergic, cholinergic and histamine receptors [13].

The latest generation of atypical antipsychotics is represented by aripiprazole, which is a partial agonist of the dopamine D2 receptor and can inhibit its function when the receptor is in its active conformation, but will stimulate the receptor in the inactive conformation [3]. These dual properties of aripiprazole are expected to improve both positive and some negative symptoms of schizophrenia, with low risk of dopaminergic side effects [3]. Recent systematic reviews suggest that aripiprazole is not more clinically effective than typical antipsychotics, but causes fewer extrapyramidal symptoms and overall seems to be tolerated better than the typical antipsychotics, however the risk of dizziness and nausea is higher with aripiprazole [14]. It should be pointed out that the risk of extrapyramidal symptoms and neuroleptic malignant syndrome is not eliminated completely with the atypical antipsychotic drugs and these agents can cause adverse effects that are seldom observed with the traditional neuroleptics: clozapine can cause hematotoxicity (agranulocytosis), while other atypical antipsychotics (as well as clozapine) can cause rapid weight gain and type II diabetes [9]. As mentioned above, most of the traditional and atypical antipsychotics are effective against positive symptoms, but have little or no effect on negative and cognitive symptoms of schizophrenia, which is one of the shortcomings of the dopamine hypothesis [15]. A large percentage of schizophrenic patients (up to 40%) do not respond to treatment with most known antipsychotics [16]. Another drawback of the dopamine hypothesis is that genetic studies of schizophrenic patients failed to identify any genes that are specifically related to dopamine or D2 receptors with the exception of the gene encoding catechol-o-methyl transferase (COMT), an enzyme that is not specific to dopamine and is involved in degradation of other catecholamines, such as adrenaline and noradrenaline [6,17]. The aforementioned genetic studies identified a couple dozen genes that may be associated with schizophrenia and many of these genes have to do with GABAergic and glutamatergic systems in the brain, which is the subject of the latest major theory of schizophrenia, as discussed next [6,17].

The newer perspective on the pathophysiology of schizophrenia is reflected in the n-methyl-d-aspartate (NMDA) receptor hypofunction theory of schizophrenia. This hypothesis was formulated based on the observation that NMDA receptor antagonists such as ketamine and phencyclidine (PCP) can cause both positive (hallucinations) and negative symptoms of schizophrenia in healthy subjects [15]. In contrast, dopaminergic drugs such as amphetamine and cocaine can reproduce only positive symptoms (and few or no negative symptoms) in humans and laboratory animals, as was mentioned above [15]. NMDA receptors are glutamate receptors located mostly postsynaptically and they are thought to play a major role in learning and memory because they are involved in mechanisms of long-term potentiation. The possible involvement of NMDA receptors in schizophrenia was puzzling at first because the behavioral symptoms induced by NMDA antagonists seemed at odds with the known function of these receptors [17]. It was later found that NMDA receptors mediate excitatory postsynaptic potentials on dendrites of inhibitory GABAergic neurons known as fast-spiking interneurons [17]. Lisman and colleagues have recently proposed a circuit-based model according to which, the fast-spiking interneurons have inhibitory projections onto pyramidal cells (glutamatergic neurons with excitatory output), which are mostly located in the cortex and hippocampus [17]. The inhibitory fast-spiking interneurons are thought to be involved in the homeostatic regulation of the activity pyramidal cells via a negative feedback loop: the

pyramidal cells have projections to the fast-spiking interneurons and these synapses (many of them contain NMDA receptors) may serve as "sensors" of the level of activity of pyramidal cells [17]. Inhibition of NMDA receptors by PCP in this system would be expected to destabilize the feedback regulation and cause excessive activity of pyramidal cells (via disinhibition), possibly leading to hallucinations and other psychotic symptoms. Experiments on laboratory animals indeed show that administration of PCP or ketamine can increase disorganized spiking activity of glutamatergic neurons projecting to the prefrontal cortex and this was determined both by measuring the glutamate efflux and by electrophysiological methods [18]. NMDA receptors are known to enhance glutamatergic transmission (via long-term potentiation) and their main ligand is glutamate, therefore it would seem that blockade of NMDA receptors should logically reduce glutamate signaling [19], but experimental data suggest that NMDA antagonists actually cause a hyperglutamatergic state at least in discrete regions of the brain [20]. Deficiencies in the signaling/metabolism of GABA (gamma-aminobutyric acid) in the fast-spiking interneurons would also be expected to contribute to psychotic symptoms according to the above model [17], and genetic linkage studies of schizophrenia have indeed identified a number of genes relevant to the GABAergic system [6].

There may also be a connection between the theorized dysregulation of the glutamate system on the one hand and the dopaminergic abnormalities in the striatum that form the basis of the dopamine hypothesis on the other hand [17]. In particular, some studies have shown that NMDA antagonists (hallucinogens such as ketamine and PCP) can increase extracellular dopamine in the striatum and there may exist another feedback loop between hippocampal pyramidal cells and dopaminergic neurons of the ventral tegmental area [21]. The readers can find an excellent review of this topic in a recent article by Lisman *et al* [17].

Various therapeutic approaches aimed at enhancing NMDA receptor function have been tested in clinical studies and the data show that these treatments can significantly reduce negative symptoms and improve cognitive symptoms in schizophrenic patients, but, unfortunately, the effect on positive symptoms is either modest or non-existent [5,19]. Since direct glutamate agonists would be excitotoxic, the above strategies are based on stimulation of NMDA receptors via an obligatory co-activator site on these receptors, which is known as a "glycine modulatory site" [19]. Activation of the NMDA receptor requires three events to occur simultaneously: 1) binding of a glutamate molecule, 2) binding of a molecule of glycine or D-serine to the glycine modulatory site, and 3) depolarization of the postsynaptic membrane [22]. Glycine reuptake inhibitors and glycine agonists such as glycine itself, d-serine, and d-cycloserine have all been shown to be effective for negative and some cognitive symptoms of schizophrenia as mentioned above, and may be beneficial as a supplementary treatment [22].

Until recently, it's been widely believed that D2 receptor inhibitory activity is absolutely mandatory for a neuroleptic drug to be clinically effective [7]. An intriguing development several years ago was the discovery of a prospective antipsychotic agent (LY404039) that has no activity at any known dopamine receptors [23]. This compound is a selective agonist of type II metabotropic glutamate receptors (mGluR2 and mGluR3) and was originally developed as a candidate antianxiety agent, since it can reduce synaptic release of glutamate. The finding that a gene called GRM3, which encodes mGluR3, is linked to schizophrenia, as well as animal studies, which showed that LY404039 can reverse many of the behavioral effects of PCP in a mouse model of schizophrenia, prompted Patil and colleagues to conduct a

clinical study of an oral prodrug (LY2140023) in schizophrenic patients [23]. That study showed that this drug can reduce positive symptoms in patients almost as effectively as olanzapine (an atypical antipsychotic), but can also improve negative symptoms. The preliminary data suggest that LY2140023 does not produce extrapyramidal symptoms, weight gain or hyperprolactinemia, which can be caused by typical and atypical antipsychotics [23]. The mechanism of action of LY404039 may seem to contradict the NMDA receptor hypofunction hypothesis of schizophrenia, since the drug tends to downregulate synaptic release of glutamate (the main agonist of NMDA receptors). Nonetheless, several studies have shown that administration of NMDA antagonists (as a model of schizophrenia) appears to cause a hyperglutamatergic state in some brain regions as was already mentioned above [21], and therefore attenuation of glutamate efflux via stimulation of mGluR2/3 would be expected to reduce psychotic symptoms [24-26]. In particular, studies in laboratory animals have shown that mGluR2/3 agonists can reduce cortical glutamate efflux caused by PCP or 5-HT2A agonists (hallucinogens) as well as inhibit dopamine release in the nucleus accumbens (ventral striatum) [24,25]. Additionally, one study showed that mGluR2/3 agonists can enhance NMDA receptor-associated postsynaptic currents in the prefrontal cortex, suggesting that these pharmacological agents can enhance NMDA receptor function in some brain regions [26]. In summary, both stimulation of mGlu2/3 receptors and enhancement of NMDA receptor function by means of glycine modulatory site agonists are novel and promising approaches to the treatment of schizophrenia and further research is necessary. The manufacturer of LY2140023, Eli Lilly, Inc. announced in April 2009 that the second trial of this compound in schizophrenia failed to show clinical benefits that are greater than the placebo effect. Further research will be needed. To summarize, pharmacological agents that act on the dopamine D2 receptors are currently the only proven type of neuroleptic drugs [5].

It is worth mentioning that there are nonpharmacological treatments for hallucinations, such as electroconvulsive therapy, repetitive transcranial magnetic stimulation (rTMS), and psychotherapy. Recent systematic reviews suggest that electroconvulsive therapy and rTMS can be beneficial [27], while cognitive-behavioral therapy is not effective against positive symptoms of schizophrenia (delusions, hallucinations and thought disorder) [28]. Among other possible nonpharmacological treatments, dietary interventions are somewhat similar in their mode of action to the pharmacological approach and, in theory, a specially designed diet could be beneficial in psychosis. At present, dietary interventions that have a proven neuroleptic effect are unknown.

This article discusses a dietary intervention and a physical treatment that may produce some of the physiological effects of neuroleptic agents that were discussed above. Hyperthermia (increased core body temperature) produces some biological effects that are similar to those of neuroleptic drugs, such as loss of motivation and hyperprolactinemia. Additionally, literature suggests that radical dietary changes can be used successfully for the treatment of some brain disorders: for example, a ketogenic diet (high-fat, protein-normal, low-carbohydrate) has been shown to be beneficial for patients with treatment-refractory epilepsy [29,30]. Recent studies suggest that a restrictive elimination diet can be effective in the treatment of attention deficit hyperactivity disorder (ADHD) [31]. Interestingly, several studies have shown that low-protein diets (and, to a lesser extent, low-fat diets) can affect the level of dopamine, serotonin, glycine, the density of dopamine D2 receptors and dopamine transporter (DAT), as well as synaptic release of glutamate in the brain as discussed in more detail below. Therefore, low-protein or protein-free diets may have psychoactive properties

that may be useful for the treatment of hallucinations. The arguments presented below attempt to show that repeated hyperthermia and a temporary protein-free diet produce effects that are similar to those of neuroleptic drugs and therefore these nonpharmacological treatments could be beneficial for patients who do not respond to existing types of neuroleptic medication. This is because patients respond differently to different classes of neuroleptic drugs and even to different drugs within the same class.

Rationale for a Temporary Protein-Free Diet

a) Some studies showed that low-protein diets can increase the plasma and brain levels of glycine without changing the levels of glutamate [32-35]. This can stimulate the activity of n-methyl-d-aspartate (NMDA) receptors and may have a therapeutic effect on negative symptoms of schizophrenia in accordance with the NMDA hypofunction hypothesis of schizophrenia [19].

b) One report showed that a low-protein diet can reduce the density of dopamine D2 receptors in the striatum of rats [36] and also reduce the total tissue level of dopamine in this brain region and in the ventral tegmental area [79]. The sensitivity of D2 receptors was not changed in that experiment. Restriction of dietary protein in humans can reduce the level of homovanillic acid, a major metabolite of dopamine, in the cerebrospinal fluid, which can be interpreted as reduced dopaminergic activity in the brain [37]. Additionally, a low-protein diet was shown to worsen coping behavior in an animal model of depression, the Porsolt swim test [38]. These alterations are suggestive of reduced dopaminergic activity in the brain and bear a resemblance to the effects of neuroleptic drugs. Most antipsychotic drugs inhibit activity of many dopamine receptors (D1, D2, D3, and D4) but their neuroleptic effect is attributed to the antagonism of cerebral dopamine D2 receptor. Neuroleptics also promote behavioral despair (worsen coping behavior) in the animal models of depression [39]. Neuroleptic drugs are also known to appreciably lower mood in human subjects within hours [40,41]. One possible problem with the argument outlined above is that neuroleptic drugs tend to increase the density of dopamine D2 receptors [42,43], and they can elevate extracellular dopamine in the relevant brain regions by inhibiting presynaptic D2 receptors [44,45]. Nevertheless, in general, neuroleptics downregulate cerebral dopamine activity via inhibition of postsynaptic dopamine receptors [46].

c) In primates, reduction of dietary protein intake can decrease the synthesis and turnover of serotonin in the brain [47]. The inhibition of both dopaminergic and serotonergic transmission in the brain by a low-protein diet may be similar to the effects of clozapine. This drug inhibits several serotonin receptors (5-HT2A, 5-HT2C, and possibly 5-HT3 and 5-HT6 [13,48-52]) and dopamine receptors (D1, D3, and D4) in addition to its moderate inhibition of D2 receptor function [13,53-56].

d) Manipulations of dietary fat have been reported to change the density of D2 receptors as well as the density of the dopamine transporter in the striatum in laboratory animals [57,58]. This observation suggests that a low-fat diet may affect the activity of the dopamine system in the brain.

e) Low-protein, low-fat, high-carbohydrate diets are rather common among mammals. Although the closest genetic relatives of humans among primates are omnivores, there are some primate species that are frugivores [59,60].

A good example of a low-protein diet is the fruit-and-vegetable diet. It contains very low amounts of fat and protein and can be considered an ancestral diet of primates [59,60]. The quality of protein in this diet is low too [61-63]. For this reason, the fruit-and-vegetable diet can be considered a "protein-free diet." For the purposes of the proposed experiment, this diet should exclude protein-rich plant foods such as nuts, grains, and legumes. This author's unpublished personal observations suggest that pungent vegetables such as garlic, onion, and horseradish may increase irritability in the context of this diet and may have to be excluded too. Up to 90% of the fruits and vegetables in this diet can be cooked at moderate temperature (by boiling or steaming). All food additives, salad dressings, and other seasonings will be excluded from the fruit-and-vegetable diet in order to facilitate interpretation of the psychotropic effects of this approach.

This author (a healthy subject) has tested the fruit-and-vegetable diet extensively on himself, but since he has never been diagnosed with a psychotic disorder, it is unknown if this approach can be effective as a neuroleptic treatment. In principle, it appears that the dietary and pharmacological approaches are not mutually exclusive and could be combined if necessary. It must be noted that the high-carbohydrate diet such as the one described above can be problematic for patients with diabetes.

Rationale for Repeated Hyperthermia

It is possible that intermittent hyperthermia has an antipsychotic effect because this approach is expected to have some neurobiological effects that are similar to those of neuroleptic drugs. It should be mentioned that hyperthermia carries a risk of serious side effects, especially when combined with neuroleptic medication. The prospective participants in this kind of clinical trial should consult with their doctor about the safety of this approach, especially participants who have a chronic medical condition and/or take any medication.

i. The dopamine system in the brain serves many functions including regulation of mood. Dopamine reuptake inhibitors such as cocaine and amphetamine can quickly elevate mood [64,65], while dopamine antagonists such as neuroleptic drugs can lower mood within hours [40,41]). Exposure to heat can quickly lower mood [66,67] possibly because this treatment inhibits dopamine activity in the brain as explained below. The mood recovers within about 60 minutes after exposure to heat is discontinued [66,67].
ii. Hyperthermia can increase the level of serotonin and serotonergic activity in the brain judging by the elevation of plasma prolactin in humans [68] and direct measurements in the brains of rodents [69,70]. The plasma concentration of prolactin is negatively regulated by dopaminergic neurons and positively regulated by serotonergic neurons [71,72]. Serotonergic neurons largely inhibit the activity of dopaminergic neurons in the mesolimbic pathway [73]. Therefore, it is possible that

hyperthermia inhibits cerebral dopamine activity. Inhibition of dopaminergic activity in the brain may be beneficial during hallucinations because the widely accepted theory of psychosis (dopamine hypothesis of schizophrenia) suggests that hallucinations and other psychotic symptoms can be caused by hyperfunction of the dopaminergic system.

iii. As mentioned above, neuroleptic drugs can lower mood [40,41] and tend to inhibit dopaminergic activity in the brain; these drugs can also raise the level of prolactin in blood plasma [71,72]. It is noteworthy that antipsychotic drugs can affect thermoregulation: one of the rare side effects of these drugs is neuroleptic malignant syndrome, which often includes the symptom of dangerously high body temperature (hyperthermia).

iv. In the past, antipsychotic drugs were often referred to as "major tranquilizers." This name implies that these drugs can tranquilize the most agitated and violent patients. Hyperthermia may also be effective as a "major tranquilizer" because high core body temperature can cause disabling fatigue and loss of motivation [74,75].

Practical aspects of using hyperthermia warrant some elaboration. Hyperthermia does not have to be maintained constantly and a temporary hyperthermia that is repeated daily (let's say, 30 minutes per day) may be effective. A convenient way to increase core body temperature is a hot bath or immersion in hot water up to the neck. This author's unpublished observations suggest that hyperthermia can induce temporary disabling fatigue if core body temperature reaches 39°C. One possible problem with hot baths is that if the temperature is relatively high (42-43°C), then this treatment can inhibit the function of T lymphocytes [76,77], i.e. it may negatively affect the immune system (blood carrying T lymphocytes passes through the overheated epidermis). Another potential problem is skin irritation if the water is too hot. Thus, the high temperature of water can induce hyperthermia relatively quickly (within 30 minutes), but may cause immunosuppression and skin irritation if it is used on a daily basis. Thus, a slower protocol may be safer. For example, water temperature can be set to 39.5°C in a bath and vigorous (automatic) stirring of water may accelerate body heating. The author (a healthy subject) did some self-experimentation with hyperthermia, but since he does not have a history of hallucinations (or psychotic disorders in general), it is currently unknown if this approach can be effective in psychosis. As mentioned above, the hyperthermia treatment cannot be combined with neuroleptic medication because this combination is unsafe [75].

Testing

An intermittent fruit-and-vegetable diet can be tested in a clinical trial with schizophrenic patients with controls who take a proven neuroleptic treatment such as olanzapine. The effectiveness of these two treatments can be compared using a symptom rating scale such as PANSS. Sample size requirements can be calculated using PASS software [78] (equivalency study design). The possible intermittent schedule of the diet can be as follows: one week of the protein-free diet, followed by two weeks of a balanced diet, then the cycle repeats and ends with one week of the protein-free diet during week 7. Although the protein-free diet is

used only intermittently, it may have lasting effects on the dopaminergic system due to neuronal plasticity.

Sessions of hyperthermia (30 minutes, 39°C core body temperature) once or twice a day can be compared to a proven neuroleptic treatment as described in the previous paragraph, except that hyperthermic treatments would be performed every day for 7 weeks.

Conclusion

At present, clinical effectiveness of the repeated hyperthermia and temporary protein-free diet is unknown. The theoretical evidence presented above suggests that these treatments may be effective against hallucinations and further research will be needed to test these ideas.

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THE TEXT BELOW IS THE AUTHOR'S UNPUBLISHED NOTES

(August 2024)

After many years of research, the author came up with a self-management system that can allow a patient with a diagnosis of schizophrenia or bipolar disorder to manage psychotic symptoms without medication or even cure the disease. The system consists of several lifestyle interventions, many of which have proven sedative effects, and in combination are expected to have a powerful tranquilizing effect [e.g., the horizontal body position (staying in bed all day), elevated air temperature, warmer clothes, a hot bath or sauna, honey, a mixture of sedative herbs, breath-holding exercises, a high-fat diet, a walk in a forest, and avoidance of all CNS stimulants, such as coffee, cacao, tea, ginseng, pungent vegetables, lemon juice, cardio exercise (e.g., climbing five flights of stairs), cold showers, and raw flesh (e.g., sushi, carpaccio, and smoked raw sausages)]. To get rid of hallucinations (without sedation), many healthy lifestyle changes are needed, and a raw diet should be helpful. Curative effects of some interventions such as the ketogenic diet and prolonged fasting are supported by published anecdotal evidence regarding schizophrenia and bipolar disorder (a number of case reports). The proposed

system has a solid theoretical basis, but rigorous clinical proof is not expected any time soon because clinical trials are expensive (modern clinical trials prove nothing anyway, as explained in this article). Nevertheless, the proposed system is free of charge, easy to try, makes sense, and is relatively safe. A patient can give it a try even without rigorous proof. Many if not most cases of bipolar disorder are a side effect of antidepressant drugs, and gradual discontinuation of all psychiatric drugs (tapering off the dose for several months) should be curative. The proposed system can also help a patient to gradually get off harmful useless drugs such as neuroleptics, i.e., to overcome their withdrawal effects. The current definition of clinical delusions is illogical and unscientific and should not be taken seriously (it may be politically motivated, intended to suppress truths inconvenient for the powers that be). The current definition of paranoia is hypocritical and unscientific too: it's OK for the government to be extremely paranoid without any evidence (e.g., counterintelligence agencies and prosecutors accusing people of a conspiracy), but a little bit of paranoia exercised by an ordinary citizen toward the government is a serious offense punishable by placement in a mental institution and forced medication. In other words, there are many false diagnoses of mental disorders. I am convinced that the government intentionally promotes an unhealthy lifestyle (that appears to be healthy) to keep the population dumb and easy to control. At present, the author believes that complex mental disorders such as schizophrenia and depression necessitate a complete overhaul of the lifestyle (several simultaneous lifestyle interventions) plus psychotherapy (there are free online versions nowadays). The self-management system is described in appendix IX of the free ebook "How to Become Smarter" (2010) which the author wrote under a pen name:
http://shevchuk-editing.com/HowToBecomeSmarter.zip

If a patient hears voices or the brain is damaged by many years of antipsychotic drugs, then a full recovery may take several years, when brain tissues are replaced with healthier ones on a new lifestyle (just like getting rid of a brain tumor via noninvasive lifestyle changes takes several years, e.g., the Gonzalez/Kelley protocol and Revici method).

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