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A KATP Channel Theory of Attention-Deficit Hyperactivity Disorder

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A KATP Channel Theory of Attention-Deficit Hyperactivity Disorder

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Abstract: I present the first complete theory of ADHD. ADHD occurs when the organism adapts to try to maintain higher glucose levels than normal. The main mechanism via which this is done is by faster opening of KATP channels, mainly Kir6.2/SUR1, which increases the cell's intrinsic excitability. I show that this induces all of the symptoms of ADHD. The optimal treatment for ADHD already exists, since drugs of the sulfonylurea family close KATP channels and have been used for safely treating people for dozens of years.

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Theory

- I present a **KATP channel theory of ADHD (K*ADHD)**. K*ADHD is the first complete theory of ADHD, explaining its etiology, symptoms, pathophysiology, and treatment. The theory is strongly supported by the evidence, and points to **a novel, immediately available, and inexpensive optimal treatment, by a non-stimulant drug**.
- According to K*ADHD, **the core cause of ADHD is chronic activation of ATP-inactivated potassium channels (KATPCs)**.
- KATPCs are inwardly-rectifying channels, and their chronic opening increases intracellular potassium. High K^+ directly excites the cell, and opposes the activation of the membrane sodium-potassium pump (Na^+/K^+-ATPase), leading to high intracellular sodium as well. The end result is chronic intrinsic cellular hyperexcitability. Thus, **cells tend to spontaneously fire without reason.**
- KATPCs are comprised of pore opening Kir6.1 or Kir6.2 subunits, and regulatory SUR1, SUR2A or SUR2B subunits. **The combination most relevant to ADHD is Kir6.2/SUR1**, which is the one expressed in fast twitch skeletal muscle, hypothalamic glucose sensing neurons, pancreas beta cells, adrenal epinephrine (EPI) and norepinephrine (NEP) neurons, heart atria, and various brain areas. The main culprit in ADHD is SUR1, which controls channel opening.
- High spontaneous firing directly explains the ADHD symptoms. **In the motor system, it manifests as hyperactivity. In cognition circuits, it manifests as inattention** (a lack of ability to sustain attention, reduced concentration), since any neural activation outside the attended paths can interfere with attention. In both types of circuits, spontaneous activation can manifest as **impulsivity**.
- There could be several reasons behind the KATP impairment. A common case is high glucose levels experienced during sensitive developmental periods, by patients or their ancestors. This can lead to persistent protein expression changes to maintain such levels, and these changes **can be heritable (e.g., via epigenetics)**. The relevant mechanisms are explained right below.
- The brain manages hypoglycemia (hypog) via **counterregulatory responses (CRRs)**. After reduced glucose levels suppress insulin secretion, CRRs include the release of pancreas glucagon, adrenal EPI, cortisol (the human glucocorticoid), and NEP, and pituitary growth hormone (GRH), which increase liver glycogenolysis and gluconeogenesis (GNG) and adipose tissue lipolyis (to produce raw materials for GNG). **CRRs (mostly their EPI part) desensitize** very quickly following repeated activation.
- KATP channels are activated by ATP deficiency, and as such are **hypog sensors**. Their opening is a major mechanism participating in the activation and execution of CRRs.

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- High glucose levels during sensitive periods stimulate adaptation to a high glucose state. When this happens, the brain attempts to maintain glucose levels that are higher than normal (i.e., glucose thresholds that trigger CRRs are higher). Faster opening of KATPCs is one way of elevating CRR thresholds. Thus, adaptation to higher glucose levels can result in faster opening of KATPCs. **This is why high glucose during sensitive periods (pre- or postnatal) is associated with ADHD**.
- When CRR thresholds are higher, CRRs are activated more frequently than normal, which can lead to their desensitization. With desensitized CRRs, there is nothing that counters hypog, so **the person is more likely to experience a hypog episode**. Hypog causes ATP deficiency, impairing the activity of the plasma membrane sodium-potassium pump even more. This further exacerbates ADHD symptoms.
- The glucose thresholds for the CRR EPI response are higher than those for the cortisol, GRH and NEP ones (i.e., EPI is triggered earlier), and the latter responses are not desensitized as strongly as the EPI one. Thus, cortisol, GRH and NEP protect from severe hypog, and **the patient experiences only mild hypog**. Hence, although ADHD patients experience hypog episodes, they normally do not show the more serious symptoms associated with hypog.
- In medical settings, blood glucose levels are normally measured in the morning after a nightly fast. At this time, circadian cortisol secretion is at its peak, and NEP levels are elevated. These compensate for the desensitized state of the EPI CRR response. **This explains why the presence of mild hypog is generally not identified**.
- ADHD patients commonly **develop obesity and type 2 diabetes (DB2) at a relatively young age**. This occurs because CRRs elevate blood free fatty acids (FFAs) via lipolysis. Chronically activated CRRs yield chronic FFAs, which is a known cause of insulin resistance. In addition, chronic cortisol release can yield cortisol resistance, which is a known cause of obesity.
- Supporting K*ADHD, **maternal obesity, DB2, and gestational diabetes increase the risk of offspring ADHD**.
- ADHD patients show **dysregulations of the sympathetic nervous system (SNS) that are consistent with chronic activity and desensitization**.
- KATPCs are strongly expressed at the **heart**. ADHD patients show increased cardiovascular disease, increased basal heart rate, and decreased vagal tone.
- People with ADHD do not show any obvious brain pathology, but there is a delay in reaching peak cortical thickness. This may be due to repeated hypog episodes during development.
- ADHD is diagnosed more in **males**. This may reflect diagnosis bias, but can also be explained by the fact that males normally have higher CRR glucose thresholds, so are more vulnerable to CRR desensitization.
- **Females with ADHD tend to be diagnosed as the inattentive rather than the hyperactive type**. This could be because in skeletal muscle, KATP channels are expressed in type IIB (fast-twitch) fibers, and these comprise a larger area of the muscle in males than in females.
- ADHD is much more common in **children** than in adults. This happens because children have higher CRR glucose thresholds than adults.
- ADHD has high comorbidity with **epilepsy**. This can be explained by the fact that potassium channel dysregulations are known to be involved in epilepsy.
- ADHD risk is higher in **preterm** babies. This may be because the secretion of progesterone, which delays birth, depends on KATPCs, so their impairment may cause preterm delivery. In addition, preterms develop hypog more easily.
- ADHD is diagnosed more in the younger children in their classes. Beyond diagnosis bias due to less mature behavior, this can be explained by the fact that in most of the world, **the youngest children in their class are conceived in colder months** than the older children. Cold induces a sympathetic response that increases blood glucose. Cold during conception, which is a highly sensitive period, explains increased ADHD risk.

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- There are indications that patients with ALS have lower incidence of childhood ADHD and ADHD symptoms. K*ADHD explains this by noting that (i) Ca^{2+} is known to be a major causal agent in ALS, and (ii) Ca^{2+} inactivates KATPCs.
- It should be kept in mind that ADHD symptoms are very general and could be triggered by several different causes. The KATP theory described here is a major such cause, but there could be others.

Treatment

- The optimal treatment for ADHD is to slow down the opening of KATPCs. Fortunately, there is an existing class of drugs with precisely this effect. **Sulfonylureas are selective KATPC blockers that have been used for treating diabetes for decades, including in children. They are inexpensive, widely available, safe, and cross the blood-brain barrier**.
- Of the sulfonylureas, gliclazide has a 16K-fold higher affinity to SUR1 over SUR2A, while glimepiride has a similar affinity to SUR1, SUR2A, and SUR2B. Gliclazide and glimepiride have a better safety profile than glibenclamide (glyburide), being associated with lower risk of insulin-induced hypog and CVD. Thus, **at this point, the first choice for treatment is gliclazide**. However, the question which of the sulfonylureas is most suitable in ADHD is an empirical one and might be personal to each patient.
- **Biomarker**. An oral glucose tolerance test (OGTT) can expose CRR desensitization in many (but not all) patients (see detailed summary of 2 references below.)

Evidence and References

Note: references for ADHD-related facts that are assumed to be known by ADHD experts are not listed here.

Potassium. There are many excellent reviews on KATPs, including blockers and openers, relationship with CVD and diabetes, etc. [1].

Importantly for ADHD, high intracellular potassium slows down the activity of the plasma membrane sodium-potassium pump (Na^+/K^+-ATPase) [2].

Potassium channels in ADHD. A genetic analysis of ADHD found potassium channels (KCs) as one of the central pathways [3]. A mutation in the Kir6.2 KATP subunit induces ADHD (as well as other symptoms) [4]. A mutation in the SUR1 KATP subunit induces ADHD (with epilepsy and insulin-induced hypog) [5]. Mutations in the Kv1.4 (shaker) and Kv4.3 KCs induce ADHD [6,7]. Kv10.1 and Kv2.1 knockout mice show hyperactivity [8,9].

K*ADHD explanations for some ADHD facts. ADHD is more common in males (also) because males have higher CRRs to moderate hypog [10]. ADHD is much less common in adults because CRR glucose thresholds are higher in children (i.e., children show the ADHD phenomenon more than adults) [11]. They are also much higher in DB2, explaining why almost one half of DB2 patients develop ADHD symptoms [12]. KATPCs have an important role in the secretion of progesterone in the female reproductive system and hence their impairment may be related to preterm delivery [13].

Direct SNS evidence. There is direct evidence for both increased and decreased (or desensitized) SNS activity in patients. For decreased SNS, one paper reported oral glucose tolerance test (OGTT) results in ADHD [14]. At 3-5 hours post glucose ingestion, when insulin-induced hypog occurs, EPI greatly increased in controls (as part of CRRs), but its increase in ADHD subjects was 50% lower. NEP did not change in controls but was reduced to 73% in ADHD. There was a trend for lower growth hormone and glucagon. Thus, all CRR components, especially EPI (i.e., SNS), are reduced.

Substantially lower urine EPI in was reported inattentives, with no NEP diffs [15]. Children and adolescents with ADHD show significantly lower basal blood pressure, which disappears after 10y [16] Patients show lower urinary DOPEG, a NEP metabolite of MAO in SNS neurons, largely from recently reuptaken NEP [17]. This can be due to decreased release, or increased uptake. There was also a trend for decreased urinary EPI. Patients showed decreased EPI, dopamine (DA) to cognitive stress

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(with higher tonic NEP, EPI) [18]. In patients, exercise yields decreased elevations of EPI, NEP, DA, and lactate. Baseline NEP is significantly lower, but both NEP and EPI are still in the normal range [19]. In a group of boys aged 13 (not diagnosed with ADHD), there was lower urinary EPI in higher aggresiveness, restlessness, concentration difficulties, and under stress [20]. In another non-diagnosed group, there was a relationship between inattention (not in patients) & lower SNS activity (longer heart pre-ejection period) [21]. In adolescent boys with externalizing problems, conduct disorder was associated with lower salivary alpha-amylase, indicating lower SNS activity [22]. Sluggish symptoms was positively associated with heart rate variability (HRV, indicating decreased SNS)[23].

Increased SNS activity was reported in many papers. Higher baseline NEP and/or EPI (with decreased EPI to cognitive stress) [18]. Higher heart rate in severe ADHD. unchanged HRV [24]. Higher heart rate, activity levels, especially in the afternoon (heart also night), in unmedicated patients [25]. 2x higher NPY in plasma and urine, with markedly increased urine NEP, serotonin (SER) metabolite [26]. Increased urinary normetanephrine (NMN), the main extracellular NEP metabolite. In patients without anxiety, lower NEP/NMN, EPI/metanephrine ratios. With anxiety, increased EPI [27]. Higher urinary NEP, DA, with NEP correlating with hyperactivity [28]. Higher urinary but not plasma NEP. EPI, DA unchanged. Lower/higher urinary MHPG/metanephrine (main EPI metab), MAO (lower platelet), zinc, magnesium (lower), GC (lower basal salivary) [29]. Higher skin conductance, basal & under stress [30]. Significantly higher salivary alpha-amylase [31]. Significantly higher pupil dilation response, with no differerence in initial or dilated diameters [32]. Reduced task-related HRV in a meta-review [33].

Increased risk for heart problems [34], and greater fatigue and sleep problems in ADHD [35–37] also point to SNS dysregulation.

(There are many more references, including for cortisol and growth hormone, supporting chronic CRRs.)

Direct glucose evidence in patients. 17.6% lower absolute brain PET glucose metabolism was reported in hyperactive girls. Significantly decreased in 6/60 regions [38] (however, this was not replicated in another study with a small number of female patients [39].) Decreased cerebral glucose metabolism in adults with hyperactivity since childhood [40].

Higher (35.7 vs 33.9, 39=preDB) but still normal HbA1c, with higher BMI and normal fasting blood glucose reported in 10-15yos [41]. Note that silent hypog (glucose<3 mmol/l) is possible with high HbA1c. This occurs in 24/11% of type 2 diabetes (DB2) patients with HbA1c </>=7% [42].

Surprisingly, I found only two papers that reported oral glucose tolerance test (OGTT) results in ADHD. In the first paper, a standard 5 hour OGTT was conducted with 265 hyperkinetic children, 211 males [43]. Glucose curves were abnormal in 74%. Among these, 50% showed flat curves, 11% showed an immediate glucose decrease following ingestion, 15% showed a rapid excessive increase, and 11% showed a similar rapid increase with a slow recovery. Flat or decreasing curves (shown in 61% of the abnormal results, or 45% of the whole cohort) indicate insulin hypersensitivity, implying chronic hypog (which induces higher insulin receptor function) and/or faster insulin secretion in almost half of the patients. Rapid increase (shown in 19% of the whole cohort) indicates reduced first phase insulin secretion, supporting higher CRR thresholds. Thus, 64% showed a pattern consistent with K*ADHD. Note that faster insulin secretion indiates lower, not higher, CRR thresholds, but would still result in hypog. Chronic hypog explains the ADHD facts, but can stem from different core causes.

In the second paper [14], following a nightly fast, a standard 5h OGTT was started in 8am. Up to 3 hours post glucose ingestion, glucose and insulin behavior were similar to controls. This shows that insulin functions normally (i.e., the body knows how to handle high glucose levels). However, at 3-5hs, when insulin-induced hypog occurs, EPI greatly increased in controls as part of CRRs, but its increase in ADHD subjects was 50% lower. NEP did not change in controls but was reduced to 73% in ADHD. There was a trend for lower growth hormone and glucagon. Thus, all CRR components, especially EPI (SNS), are reduced.

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Dopamine. DA is a NEP precursor, so according to K*ADHD, it is probably chronically released and desensitized in ADHD. There is evidence that this is indeed the case [44–49].

Patient diet consistent with glucose need. Patients consume more sugar-rich and saturated fat-rich food, and this correlates with symptoms [50]. Children and adolescents with ADHD consume more candy & fruit gum (sweets). Consumption is associated with hyperactivity [51]. Positive association between sugar consumption, sugar beverages & symptoms in a meta-review [52]. Higher risk with processed & snack diets, n=14,912, China [53]. Inattention (also hyperactivity, weaker) correlates with high sugar, fat, protein, sea food diet in 18K Swedish twins [54]. Sweetened beverage consumption associated with self-reported hyperactivity, inattention symptoms in youth [55]. Higher/lower intake of sugary, high fat foods/vegetables, fruits, protein-rich foods. n=216, Taiwan [56]. ADHD patients show poorer dental health, higher sugary food consumption [57,58].

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