Adderall and Academia: How Amphetamine binds in the Human Norepinephrine Transporter Protein

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Drug Discovery and Design in the Digital Age

Abstract

Recently, there has been a drastic increase in the use of prescription stimulants by healthy individuals in academia – specifically with undergraduate college students. We wanted to answer why this was phenomenon was occurring. Are there cognitive benefits from taking stimulants when there is no medical need and are these benefits why students are drawn to them? Amphetamine or Adderall™ is a popular misused stimulant and serves as an example to explore this issue. The first question to answer was how amphetamine is processed in the brain. Our chosen transporter was the human norepinephrine transporter (hNET) protein. This transporter controls the uptake and reuptake of both dopamine (DA) and norepinephrine (NE). The unbalance of these two neurotransmitters are believed to play a major role in Attention-Deficit Hyperactivity Disorder (ADHD). hNET is often a main target in research studies because of this. To analyze the interaction of amphetamine and NET we built a human 3D model through a process known as homology modeling and docked amphetamine, NE, and DA into it. We found that amphetamine successfully binds in the hNET binding cavity. In impaired individuals this means that amphetamine does in fact have positive benefits. However, the effect on healthy individuals is still unknown. Further research needs to be done to determine whether or not healthy individuals experience any benefits before we can answer why undergraduate college students are misusing the drug.

Introduction

Over the past 20 years, an increasing number of individuals have been misusing medical stimulants not prescribed to them. In the last decade, there has specifically been a growing number of college students taking non-prescription stimulants (Zuvekas and Vitiello 2011). These stimulants are the second most used drug, behind marijuana, by undergraduate students. Information from a 2002 survey of a US college, showed that 35.5% of undergraduates were using stimulants not prescribed to them. The students who misuse these stimulants mainly received the drug from a friend, who has a prescription for the medication. A 2008 study stated that 16% to 29% of students with prescriptions will be asked to distribute their stimulant medication at least once in their lifetime. Additionally, it was reported that 54% of college students with a prescription were confronted to buy or trade for their stimulant medication. As a result, 29% actually sold or traded their prescription. (Lakhan, 2012)

Overall, evidence suggests that white male college fraternity members with low grades are more likely to misuse stimulants. Also, misuse was seen more in the northeast part of the US, where there are many competitive

universities. A study was also done to see statistics of the use of the stimulant, amphetamine, in the medical students. The survey found that 10% of these students used this medication for academic performance. Of students using amphetamine, 5.5% had a prescription and of that percentage 72.2 % were prescribed the medicine after the age of 18. There is now a growing issue of more people pushing to be diagnosed in college to easily access these performance enhancing medications. (Lakhan, 2012)

Stimulants like amphetamine can be misused for many different reasons, even by students with a prescription. A survey showed that 25% of students with a prescription used the drugs to experience a euphoric feeling. However, stimulants, like amphetamine are most commonly used to increase academic performance. Many students communicate that stimulants are helpful, which increases the risk for others to misuse these drugs because of the positive remarks. There are many academic pressures that attribute to this issue: succeed in classes, study more efficiently, sleep, and social pressures are also factors. However, a 2011 survey stated that 93.5% of students used these drugs to concentrate and focus while studying. (Lakhan, 2012)

Many people who are prescribed and benefit from these stimulants, have Attention Deficit Hyperactivity Disorder (ADHD). This is defined as impaired information processing, memory, attention, and reaction time. By using stimulants like amphetamine these diagnosed individuals are able to increase academic productivity. It can help with finishing homework and taking notes. Although it helps with academic performance, it does not help a person learn more or increase their knowledge. Many studies found that students with ADHD did have lower grades and lower IQ scores. However, in some cases, stimulants did help those individuals increase their IQ score. In a 2008 study, the use of computerized neurocognitive screening was used to compare untreated ADHD patients with treated ADHD patients. Many differences were seen between the performance of the groups. Treated patients significantly did better than untreated patients but were still below non-ADHD subjects. Another study also showed, that stimulants significantly helped reduce disruptive behavior, but not necessarily academic performance from an intelligence standpoint (Advokat 2008). (Lakhan, 2012)

Because students recognize that stimulants do help those with ADHD, it has increased non-prescription stimulant use in college students. Many students will fake symptoms of ADHD to receive drugs like amphetamine. The media has increased the want for these drugs by mentioning benefits of using stimulants 95% of the time, while discussing the risks only 58% of the time. Colleges, like Duke University, have established policies stating, “the unauthorized use of prescription medication to enhance academic performance has been added to the definition of Cheating.” However, they have enacted this policy assuming it does lead to cognitive improvements. This was put to the test in many different studies. In a 2011 study, healthy subjects on stimulants and not on

stimulants were asked to memorize words and recall the words after a hour and a week. The stimulant group showed improved recollection for the one-week recall period, but not the one-hour period. This shows that stimulants are not useful when cramming for an exam, because short term memory is not enhanced with stimulants. A 2009 study showed that a high-performing person without ADHD symptoms will see little effects of the stimulants because these drugs do not improve intelligence (Smith, 2011). Also, in another 2011 study, the researchers examined the effects of using the stimulant as a healthy individual using a double-blind placebo trial. It showed that people who thought that they received the drug believed they were engaged and focused. However, those who thought they weren't getting the drug showed disruptive attention. Collectively, these studies show that the misuse of stimulants like amphetamine have not shown evidence to improve intelligence in healthy individuals. Instead, these stimulants slightly improve long term memory, but mostly just give off a euphoric feeling, which leads to a placebo effect in healthy individuals. (Lakhan, 2012)

While the cognitive and attention benefits of amphetamine are clear for those with ADHD, effects on cognitive abilities in healthy individuals is unclear. If college undergraduate students are using amphetamine or other stimulants to increase their academic performance, then it is important to address whether they are helping or hurting themselves.

A study done in 2008 (Farah et al.) examines this relationship between amphetamine and creativity in non-prescribed users. The researchers used a sample of sixteen adults, four men and twelve women, who were the between 21 and 30 years of age. Each participant took what looked like the same pill, but half took a placebo and the other half amphetamine. The participants then went on to take four tests: Remote Association Task, Group Embedded Figures Task, Alternative Uses Task, and Drawing Task from the Abbreviated Torrance Test for Adults. Overall, the results demonstrated that amphetamine had an insignificant effect on the participant performance. Only in the group embedded figures task did the amphetamine induced participants performance increase. What the researchers looked at next was individual performance and how an individual's baseline creativity affected the stimulants level of enhancement. By doing a regression analysis, they predicted that a lower placebo performance will result in a larger stimulant enhancement. The results for the two convergent tasks supported this. The authors do note that they should have recorded a second placebo for a baseline, but the statistical relationship was still strong enough to support the claim that amphetamine had a greater effect on lower performing participants. Their data from the remote association task illustrated a possibility that amphetamine may be detrimental to higher performing individuals, but this study itself was not enough to be conclusive.

Another study in 2012 (Ilieva et al.), was also interested in the claim that amphetamine is more effective in lower performing

individuals, but not just creativity, in general cognitive abilities too. This study operated in the same way as the previous study discussed, a double-blind placebo, and a ran thirteen tests (including the previous four). These researchers did establish a baseline for each participant and found no data to support a higher effectivity of amphetamine in lower performing individuals. However, they did find the same result as Farah: in a healthy young adult the effects of amphetamine at a medically prescribed dosage are negligible.

The question is what is going on in the brain to cause the different effects in ADHD versus healthy individuals? The human norepinephrine transporter (NET) is the common target for amphetamine and other stimulant-like medication. NET regulates catecholamine extracellular activity and due to this is strongly linked to ADHD. An intermediate level of catecholamine has been found to be optimal for memory and motor function and a problem with NET will disrupt the catecholamine extracellular levels (Hahn et al., 2009). However, the pathogenesis of ADHD is complex and much of the functional elements of the brain pathways involved are unknown. [Dopamine (DA) also plays a role, as does norepinephrine]. This is also why NET is the primary target candidate: NET controls the reuptake of both transmitters.

In a study done on rats (Marshall et al., 2019), researchers designed a selective small molecule, SK609. They made it specifically to inhibit NET. They were successful and the inhibition of NET in the rats demonstrated an increase in sustained attention. The molecule also caused an efflux of catecholamine levels and an increase in DA and NE levels. Overall, these effects lead to an increase of cognitive levels. They also concluded that the level of cognitive enhancement induced by SK609 depended on the baseline cognitive levels of each rat. This study, while done on rats, is a good example of how and why NET is a common target when it comes to designing a drug to treat ADHD.

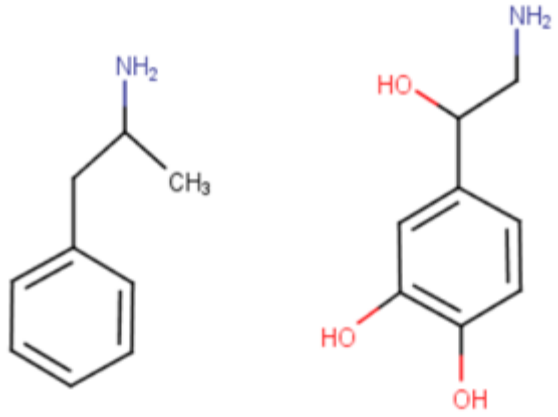

Figure 1. A two-dimensional representation of amphetamine (AdderallTM) (left) and norepinephrine (right). Generated using MarvinSketch Version, 19.4. (Marvin 2019).

Amphetamine and the native ligand, norepinephrine for hNET, are structurally similar (Figure 1). They both have a cyclohexane and a Nitrogen group. The structure similarity is what allows amphetamine to effectively bind to NET. Amphetamine is still able to bind in healthy individuals, but only gives a euphoric feeling, which is a different effect than what is seen in impaired individuals. Overall, this is the reason for the misuse of stimulants, because people mistake the euphoric feeling and confidence boost as increased cognitive ability.

The increase of amphetamine misuse in college undergraduate students is evident as many sources discussed. Studies show that this is due to academic pressures, easy access to stimulants, and the promotion of amphetamine by their peers. However, further research has shown that stimulants do not improve intelligence or creativity overall for healthy individuals. Those with impairments use stimulants to help with the reuptake of dopamine and norepinephrine. However, since healthy individuals already have a healthy concentration of these neurotransmitters, it only creates a sensation of euphoria, which leads to a placebo-like effect on mental performance. Therefore, if college students use stimulants like amphetamine, specifically for academic performance enhancement, there will be physical results for subjects with impaired processes in the brain. However, subjects without impairments will only have psychological effects and an increase in confidence. By understanding the biochemical effect, subjects without impairment may have a different perception of the drug and chose not to misuse stimulant.

Methods

Data Collection from Mutagenesis Studies

Before we could start doing our homology modeling and docking, we needed information on the essential amino acids in the human norepinephrine transporter (hNET) binding cavity. We reviewed published mutagenesis studies. A mutagenesis study is when researchers create mutations in an organism's genetic sequence and see if a certain reaction still occurs. By doing this they can discern which amino acids are essential and their specific functions. In hNET, there are two potential binding cavities in the human norepinephrine transporter. Within the first cavity, three residues have been found to be essential amino acids: SER 419, SER 420, and GLY 149. The second cavity only had one known key residue – GLY 478.

Homology Modeling

On the RCSB PDB Protein Data bank, the site only provides the structure of NET in bacteria and animals (H.M. Berman 2000). Because a human NET structure is not available, it is useful to make a model to study the protein. A human model could help to identify what amino acids Adderall ™ binds to and where in the binding cavity, in order to understand how the drug can mimic the reuptake of norepinephrine. Although we do not have a model, we can access other protein sequences to find a similar model. To measure the similarity between the two sequences, we will analyze homologous protein sequences. These sequences would have similar amino acids and they would also be in a similar order. We would look at percent identity calculation, by dividing the similar residues/total residues. This shows how many amino acids are similar. There will potentially be gaps where only parts of the sequence are the same.

To build a human NET protein, we will use an online site called SWISS-MODEL (Waterhouse 2018). The site will compare the

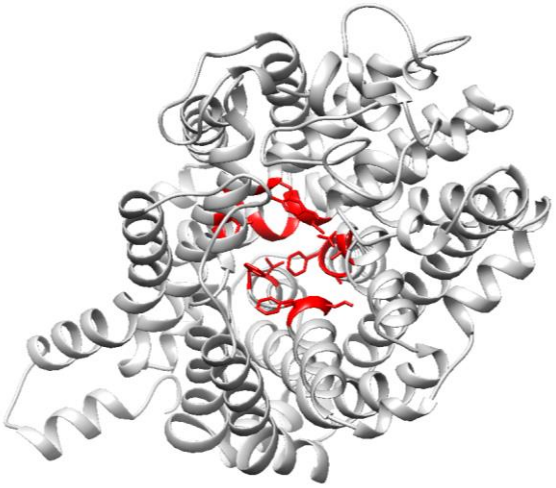

Figure 2. hNET Binding Cavity. Highlighted in red are the amino acids that make up the inner binding cavity

human NET sequence we have and give us a few templates. By analyzing the statistics of these templates, it will help to build our model. We will make our model by uploading our target sequence of human NET to search for templates that are similar. From our template results, we will look at the amount of coverage, the identity number and the global quality estimate statistics. For example, we will look at the QMEAN and the Torsion values. All values should be above -4, if it is a good model. We will not use templates with errors because those templates will most likely not work. We will also look at the quaternary structure analysis to pick the best templates. We will then also need a 3D model of amphetamine to proceed with our study. A tool called Marvin Sketch will use the built 2D structure of Adderall ™ and make a 3D model (Marvin 2019). We will then use our two new models to continue analyzing our structures (Waterhouse 2018).

Docking Process

With our homology model of the Human NET, we docked three small molecules into the binding cavity: norepinephrine, dopamine, and amphetamine. Norepinephrine and dopamine are the native ligands, while amphetamine only uses the same binding cavity. The purpose of docking norepinephrine and dopamine is so we can have an accurate depiction of where Adderall ™ is supposed to bind. We will compare the orientation of each ligand, what is binding to what, and the distance in angstroms of each binding interaction.

Table 1. Amino Acids in Norepinephrine Binding Cavity

Transmembrane Helices	**HNET**
TMH1	PHE 72
	ALA 73
	ASP 75
	ALA 77
TMH3	ALA 145
	VAL148
	GLY 149
	TYR 152
TMH6	PHE 317
	SER 318
	GLY 320
	PHE 323
	VAL 325
TMH8	SER 419
	SER 420
	GLY 422
	GLY 423

The docking itself was done with three different software programs: AutoDock Tools (Morris 2009), AutoDock Vina (O.Trott 2010), and UCSF Chimera (UCSF 2004). These software simulate where the ligands will bind and give data on all the potential binding sites. We focused on the first and inner binding cavity of hNET because our model was more reliable in the center. When making our docking box we focused it around these our key residues: SER 419, SER 420, and GLY 149. To make sure our box was as accurate as possible, it helped to highlight all of the amino acids (**Table 1.**) in the binding cavity and fit them inside the box too. The center coordinates we used for the box were 203.75 (x), 281.968 (y), and 25.628 (z). The magnitude of x, y, and z respectively were: 16, 20, and 16.

Analysis of Docking Results

After we docked amphetamine, norepinephrine, and dopamine in the binding cavity, it was uncertain whether potential interactions will be identified. Even the ligand with the highest affinity may not have been in the correct orientation or closest enough to the key residues. To determine the success of the docking we record the distances, in angstroms (Å), between carbon atoms of the ligand and key residues and of hydrogen bond interactions. For a successful hydrophobic interaction, the distance needed to be less than or equal to 3.9 Å; the distance for a hydrogen bond interaction needed to be less than or equal to 3.3 Å (Lewis et al., 2011). By knowing whether our docking was successful, we could continue and evaluate with the information from other studies to determine what is occurring in the brain.

Results

Homology Results

A human model of NET was not available at the time of this study. Therefore, Swiss-Model was used to identify homologous sequences for development of a 3D model. The template search showed low identity values, for the suggested structures. For example, one of the dopamine transporters had an identity of 59. The global quality model estimate (QMQE) was also low at .77 and the sequence similarity was also low at .48. It is best if these values are close to 1. Also, in terms of the global quality estimate, the QMEAN score was at -4.15. The Cβ score, the interaction of Cβ atoms and the All Atom score, the interaction between all atoms, had a score of -2.73 and -1.86 respectively. Any values near -4 showed that the model was very unreliable. Although, solvation of this model had a good score of 1.31, having one good quality does not define the model. (Waterhouse 2018)

This model was refined using the 3Drefine server (Debswapna 2012), which performs energy minimization on the structures to reduce clashes that translate to a lower quality model. We chose the top result from 3Drefine and used the structure assessment tools in Swiss-Model on the energy minimized model. Unfortunately this model also had a low QMEAN score at -3.19, which only slightly improved model reliability.

However, by looking at the mutagenesis studies and we understood where the essential amino acids were in the binding cavity. We were able to locate and visualize the amino acids in Chimera. This was helpful when we looked at the new model from

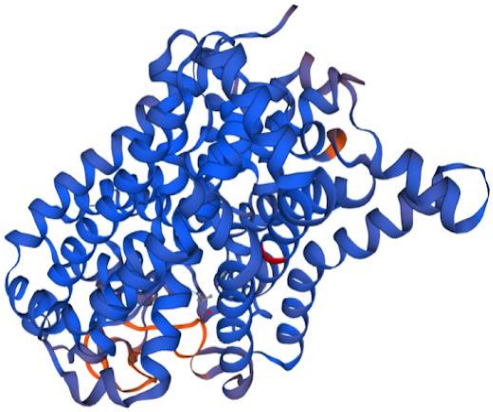

Figure 4. The final homology model of hNET. Areas of helices shaded red-orange are unreliable.

3Drefine in the structure assessment. We were able to compare the images and see that the clashes did not occur near the amino acids. Because of this, we chose the model to continue our studies and find my more information through docking. (UCSF 2004)

Docking Results

The first small molecule we docked was Norepinephrine. The best result yielded an affinity of -6.5 kilocalorie per mole (kcal/mol). Dopamine resulted in an affinity of -6.3 kcal/mol. The final and the ligand under investigation we docked was Amphetamine. Its best result was also -6.5 kcal/mol. The dopamine affinities were lower than both amphetamine and norepinephrine. This is perfectly fine because the purpose of using multiple other small molecules was to have multiple models to compare how amphetamine should bind in the cavity. Norepinephrine is the native ligand to the human norepinephrine transporter and was expected to yield the best results. However, amphetamine matched those results and its second-best model was also -6.5 kcal/mol compared to norepinephrine second model of

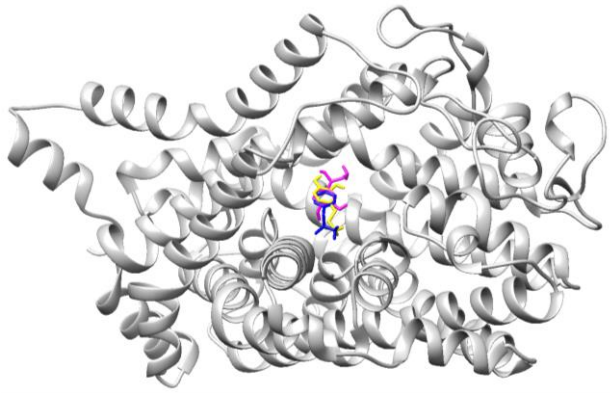

Figure 3. Docking results of Amphetamine (blue), Norepinephrine (Magenta) and Dopamine (yellow)

-6.4 kcal/mol. The fact that the amphetamine results match well with the norepinephrine results is an indicator that our models and docking is accurate.
The next step was to measure the distances of each hydrogen and hydrophobic bond.

Surprisingly, the distance results for norepinephrine and dopamine were less successful than amphetamine. For Dopamine, all hydrophobic interaction – carbon and any residue – met the threshold of 3.9 angstroms. Only N1 with SER 419 and ASP 75 met the distance requirement of 3.3 angstroms or less. The distance results of norepinephrine only predicted three bonds to be successful: C7 and PHE 323 (hydrophobic); N1, SER 420 and O2, SER 419 (hydrogen bonds). Amphetamine's distance results predicted all the bond interactions to be successful. Also, all residues that bind with amphetamine are shared with either norepinephrine or dopamine. Both of these results indicate that our docking was successful.

Table 2 Distance measurements for docking.

Atom 1	Atom 2	Distance (angstroms)
Dopamine		
N1	ASP 75 OD2	3.154
N1	SER 419 HG	2.736
O2	VAL 148 CB	3.752
O2	ALA 145 CB	3.683
C1	TYR 152 CE2	3.855
C4	TYR 152 CD1	3.78
C7	PHE 323 CE1	3.838
Norepinephrine		
N1	SER 420 OG	2.86
O1	VAL 148 CB	3.596
O2	SER 419 CB	3.299
O3	PHE 72 CE1	3.732
O3	PHE 323 CE2	3.424
C7	PHE 323 CD1	3.675
Amphetamine		
N1	SER 419 HG	2.798
C1	PHE 72 CE1	3.558
C4	PHE 72 CZ	3.715
C6	PHE 323 CE2	3.767
C7	TYR 152 CD1	3.79
C9	VAL 148 CG1	3.754

Discussion

There has been many alarming statistics about the misuse of stimulants like amphetamine. The popularity of the drug among undiagnosed individuals, specifically in a college environment is growing. Many students who misuse the drug are not aware of the health risks and the biological impacts of stimulants. Previous studies compare the behavior of healthy versus impaired individuals with amphetamine (Ilieva et al., 2012), though, none have examined the difference between the function of healthy and impaired human neuro-transporter proteins. These behavior studies point in the direction that amphetamine and such stimulants have little to no, or even a negative, effect on healthy individuals, but nothing has been done to make an assertive claim.

We hope our research can educate students. Important information found in our research has allowed us to have a better understand of how and where amphetamine binds. The results from the homology modeling and docking predicts that amphetamine binds to NET in the human brain. This means that amphetamine does have a profound effect on impaired individuals whose levels of dopamine and norepinephrine are low. However, from our research nothing can be concluded about amphetamine and healthy individuals.

We suspect that what is occurring in the brain is somewhat of an overload effect. Amphetamine still increases levels of NE and DA in healthy individuals, but only increases these levels a small amount. However, it is difficult to say who is an impair or healthy individual. Amphetamine can have different effects on different types of people. For example, if an individual has an underlying mental illness their reaction to the simulant would be have a different effect (Llieva 2015).

The future use of amphetamine and stimulants is still up in the air. The problematic increase of abuse in college undergraduate students and academia in general has been given little attention. There are plenty of positive short-term effects, but there are several more negative short-term effects and long-term effects are still widely unknown. It is always a risk to interfere with the natural functions of one's brain and users need to be aware of the possible detrimental outcomes. If there is no real cognitive benefit,

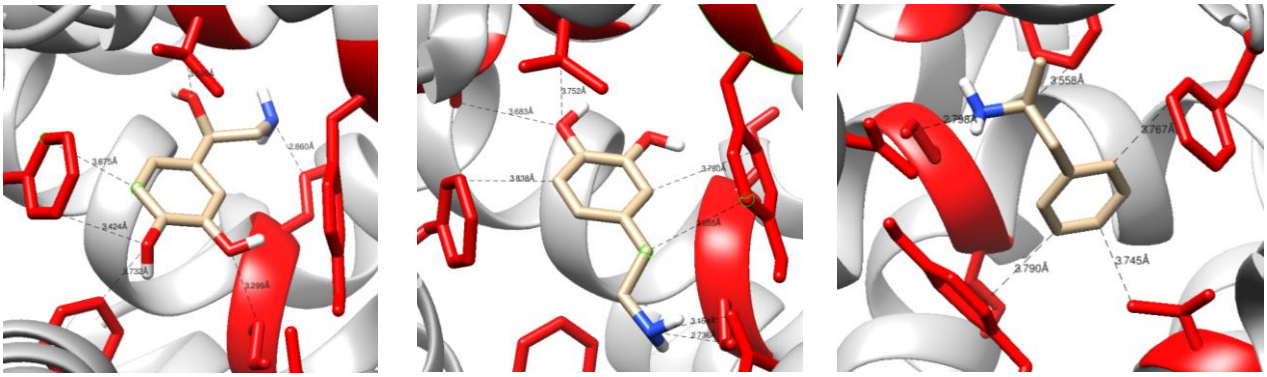

Figure 5 Distance Results of Norepinephrine (left), Amphetamine (middle), and Dopamine (right).

then no healthy individual should abuse them. If stimulants are overall safe for use and the benefits are real, stimulants would be abused by people who can afford them and create even more inequality in the world. Is it ethical to use essentially a cognitive steroid? There are almost endless questions and concerns that branch from whether or not stimulants affect healthy individuals. The answer to these questions will affect everyone on an individual level and society as a whole.

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