

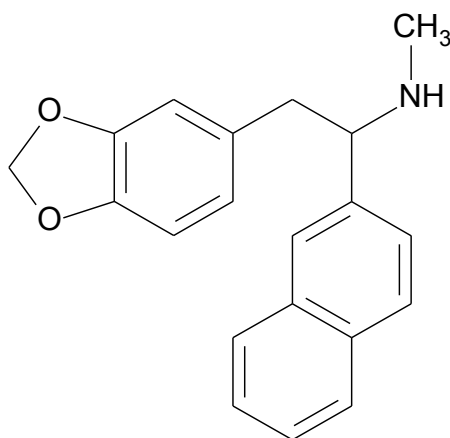
Can MDMA analogues be used in cancer treatment?

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Abstract

Based on findings in the article “Redesigning the designer drug ecstasy: non-psychoactive MDMA analogues exhibiting Burkitt’s lymphoma” (J. Gordon et al., 2010) we wanted to study how MDMA worked, and how it can be used as a treatment for cancer. The study was made based on MDMA’s ability to kill Burkitt’s lymphoma cells, by stimulating serotonin release that stimulate the pro apoptotic BCL-2 proteins so the Burkitt’s lymphoma cells goes into apoptosis.

Because of MDMA’s neurotoxicity and psychoactivity the study tested different MDMA analogues that ruled out neurotoxicity and psychoactivity. Furthermore they tested analogues which were more effective in killing the cancer cells, so a much lower dose was needed.

The report includes background knowledge about cancer, what cancer is and does and how different cancers are treated. It will also include background knowledge about MDMA, how it works and what it does. It will describe how the analogues works and how it is related to serotonin, BCL-2 proteins and the Burkitt’s lymphoma cells. It showed that there is a good opportunity that MDMA analogues in the future can be a substitute for treatment of some cancers. If psychoactivity and neurotoxicity can be ruled out, the side effects compared to chemotherapy for example, would be almost none.

Introduction

According to a recent study “Redesigning the designer drug ecstasy: non-psychoactive MDMA analogues exhibiting Burkitt's lymphoma” (J. Gordon et al., 2010), analogues of MDMA might have a chapter of it's own in the fight against certain types of blood cancer.

By experimenting in vitro, using leukaemia, lymphoma and myeloma cells (J. Gordon et al., 2010), scientist could observe the effectiveness of MDMA against cancer cells, stating they have increased it's effectiveness 100-fold (J. Gordon et al., 2010).

A research at the University of Birmingham showed the potential of MDMA and anti-depressants, as Prozac, to start apoptosis in Burkitt's lymphoma (BL) cells. (J. Gordon et al., 2005) But due to the neurotoxicity, the required dose to kill all cancer cells with MDMA would lead to fatalities (J. Gordon et al., 2010). In collaboration with the Western Australia University, researchers have chemically modified MDMA by

removing a methyl group and replacing it with various other groups. As a result of this chemically altering of MDMA, one variant increased its effectiveness a 100-fold.

That would mean that 100 times less of the MDMA-analogue is needed compared to MDMA to obtain the same cytotoxic effect. And in addition to that, the found compound had a reduced neurotoxicity (J. Gordon et al., 2010).

Professor John Gordon from Birmingham University stated, to the BBC: "Against the cancers, particularly the leukaemia, the lymphoma and the myeloma, where we've tested these new compounds we can wipe out 100% of the cancer cells in some cases." (J. Gallagher, 2010)

The alteration of the structure of MDMA made it more successful against some cancers, because the specific cancer cells had a larger amount of BCL-2 proteins. It is not yet possible to administrate MDMA analogues to patients affected by cancer, probably only in a few decades as these analogues have only been tested in vitro. To be certain that a MDMA analogue can be administrated to cancer patients, experiments on animals and clinical trials will be needed to test the efficiency of this product. As stated by Dr. David Grant, scientific director of the charity Leukemia and Lymphoma Research: "The prospect of being able to target blood cancer with a drug derived from ecstasy is a genuinely exciting proposition. Many types of lymphoma remain hard to treat and non-toxic drugs which are both effective and have few side effects are desperately needed." (University of Birmingham 2011) MDMA analogues may be a solution for cancer treatment, as cancer treatment nowadays is not safe guarding a 100% success and carrying various side effects like for example Chemotherapy has. Chemotherapy consists out of the use of chemical agents to stop cancer cells growth and/or killing these cells. But this treatment carries various side effects as: low blood cell count, nausea, vomiting, hair loss, fatigue, etc. By using MDMA analogues, it applies to Chemotherapy treatment.

Problem Formulation

Our main focus is if MDMA analogues can be used as cancer treatment. To answer the question we need to know how MDMA works in general, and how it relates to killing the cancer cells.

MDMA is neurotoxic and psychoactive, can this be ruled out by making analogues of MDMA?

If it was possible to rule out the neurotoxicity and psychoactivity, would the analogues then be able to kill the cancer cells?

At the initial research it showed that a large amount of MDMA was needed to kill the cancer cells, can MDMA be altered so the cytotoxicity is more effective?

If MDMA analogues can be taken as a treatment for cancer, would it then have less side effects than other cancer treatments, like for example chemotherapy.

If so, will the side effects weigh out the side effects from chemotherapy and surgery?

Method

The project consists of literature research as it is a very recent discovery that is still being worked on, where the study of articles related to the subject is the main foundation of this report. The conclusion will be based on a discussion about the data gathered, leading us to an answer to our problem formulation.

First of all we want to get an understanding of how MDMA analogues can be used as a treatment for cancer. Then we will go further into how MDMA is related to the cancer cells, how it actually kills the cancer cells, and how it is related to serotonin levels and BCL-2 protein. We will discuss the effects of MDMA and other cancer treatments, and compare them with each other, to conclude if MDMA analogues would be a better treatment for cancer.

Social Relevance

Our project is relevant to the semester theme because it's about a cheaper and better accessible way to cure Burkitt's lymphoma (BL) which is the most prominent cancer in young people. The cure usually involves heavy chemotherapy and has a 80% of succeeding. But not everywhere in world this kind of treatment is readily accessible and affordable. BL has a higher incidence in the BL belt, which stretches from west to east Africa near equator because of Malaria and AIDS, the last one brings complications with chemotherapy (WHO, 2007). Although the frequency at which BL occurs is only 0.005-0.020% per year. Though putting this into perspective with the amount of people living in the BL belt, which is more than half a million, it still is accountable for 25,000 - 100.000 cases a year (J. Gordon et al., 2010).

Therefore it would be helpful for the less fortunate people that there would be a alternative more accessible way of curing this disease. The way to treat people would

be taking in a dose of the MDMA analogue, might this be intravenous or oral, and would be a more humane way to treat BL. As well the research gives a good future perspective on maybe deriving a cure for more types of cancer than just BL. Especially the myeloma types of cancer seem to have interesting perspective. Which makes it very relevant for society, since what if no one would ever have to go through the treatment of conventional chemotherapy with it's many sever side effects?

Background

Cancer

When in our system a uncontrolled cell growth happens, we define it as cancer, whose process is denominated as carcinogenesis. Cancer cells affect a determined spot before spreading to the surrounding tissue to get to the blood vessels, using the vessels as a conduit to spread.

Genes and chromosomes affected by cancer will have their “program” changed due to a disorganization caused by cancer. It has been often observed an unusual and undifferentiated pattern on cancer cells, described as a lost of functionality, failing to fully develop the characteristics and proper activities of mature cells. Remarkably, metastatic cancer cells gain new functions, gaining characteristics unrelated to the normal sedentary cell type. (P. Dash, 2007)

The Cell Cycle

The cell cycle begins when a cell (the parent cell) divides into two cells (daughter cells), and ends when the daughter cells divide and also become parent cells. It is clearly seen under a microscope, and described in illustration 1. The mitotic phase, also called the M phase consists of two events, mitosis which is the division of the nucleus, and cytokinesis which is the division of the cytoplasm. At Gap 1, also called

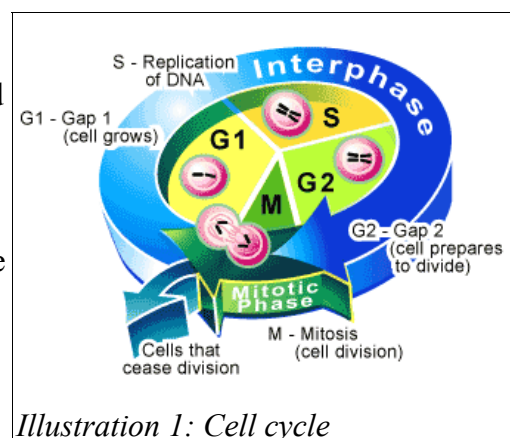


Illustration 1: Cell cycle

G1 phase, the cell grows and the cell prepares for DNA synthesis and production of histones. The time the G1 phase lasts, is variable. Growing mammalian cells can spend 8-10 hours in the G1 phase, but a cellular decision can cause the cell to enter

the G₀ state, which will stop further cell growth. After the G₁ phase, the cell is prepared to go into S-phase. Here the DNA replication takes place by condensation of the chromatin, which leaves two copies of each chromosome attached at the centromere, this is called sister chromatids. Then the cell goes into Gap 2, also called the G₂ phase. In this phase the cell prepares for division. The nuclear envelope fragments and the microtubules of the mitotic spindle separates the sister chromatids and places them in each end of the cell. This phase is usually shorter than G₁, and normally takes 4-6 hours. Cytokinesis and reformation of the nuclear membranes completes the cell division, and the cycle repeats. (W. M. Becker et al., 2008).

Cell Death: Necrosis vs. Apoptosis

Most eukaryotic cells are genetically programmed for cell death, or apoptosis. Apoptosis, or programmed cell death, occurs as a cell's defence for the development and health of multi cellular organisms. Due to a variety of stimuli that the cells might undergo, the cells become more "sensitive" such as they might die or go through apoptosis. This makes apoptosis distinct from another form of cell death called necrosis in which uncontrolled cell death leads to lysis of cells, inflammatory responses and, potentially, to serious health problems.

Some factors like injuries, bacterial toxins or even nutrition deprivation can commit the cell to undergo through necrosis. Usually toxins that are secreted by bacteria may disrupt internal or external structure and functions in a result: the cell loses functional control, osmotic pressure causes swelling in organelles, the chromatin clumps and the cell eventually bursts. Cytotoxic cellular components spill out from the membrane inducing tissue damage and inflammation.

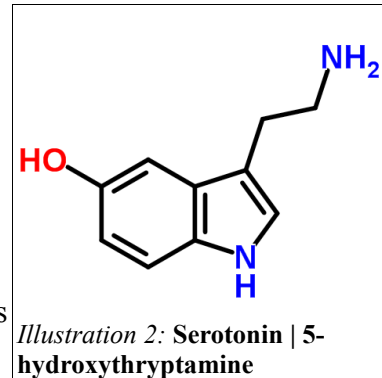
Molecular signals continually inhibit or promote this process. Bcl-2 protein is an inhibitor of apoptosis which is located on the outer mitochondrial membrane. If Bcl-2 gets deactivated then apoptosis is being initiated through a well-controlled chain of enzymatic reactions. Catabolic processes begin throughout the cell. Enzymes digest cytosolic components and fragment the nuclear DNA. Specialized cysteine proteases called caspases, target specific proteins in the nuclear lamina and cytoskeleton. The cell is repackaged for safe removal. The chromatin condenses; the cell shrinks and fragments into small membrane-bound apoptotic bodies. Finally, the compacted cell is phagocytized by adjoining cells. Maintaining the proper number of cells in any tissue

requires a delicate balance between cellular production and elimination. Essential to this balance is apoptotic cell loss on one hand and cell division on the other. When an excess of cells is produced by unrestrained cell division, or when too few cells are eliminated by apoptosis, an excess of cells accumulates in the tissue. This basically describes the situation in cancer. Cells on their way to becoming cancerous accumulate a number of genetic and chromosomal abnormalities, each of which in some way pushes the cell further in the direction of unrestricted growth. At first, clusters of genetically identical cells are formed, each cell dividing with less restraint than its normal neighbours. Some viruses associated with cancers use tricks to prevent apoptosis of the cells they have transformed. Even cancer cells produced without the participation of viruses may have tricks to avoid apoptosis. High levels of apoptotic inhibitors follow when the BCL-2 gene, when it gets translocated into an enhancer region for antibody production. Some B-cell leukaemia and lymphomas express high levels of Bcl-2, thus blocking apoptotic signals they may receive. (R. A. Goldsby et al., 2000)

Is serotonin connected with Bcl-2?

In order to find if there is a connection between serotonin and Bcl-2 we first have to make clear what exactly serotonin and Bcl-2 are. Serotonin or else 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter that is primarily located into the gastrointestinal tract, platelets and the central nervous system (CNS). It is widely known to be the main influence over several brain functions for example

control of perception, cognition, sleep, appetite, pain, and mood. Serotonin uses specialized signaling pathways (interactions with receptors that are located in the CNS and PNS) to mediate biological functions. (Science Daily, 2010) As it was mentioned before BCL-2 is a proto-oncogene that is located on chromosome 18. As a result of DNA translation, BCL-2 gives an integral membrane protein (Bcl-2) that is located mainly in intracellular compartments.



High levels of the Bcl-2 protein protect B cells (such as lymphocytes) from early apoptotic death by preventing the activation of caspases that carry out apoptosis. Sometimes BCL-2 locus goes through a reciprocal translocation that gives rise to a malignant clone of B cells. That is the reason why this translocation can be found in B-cell leukemia and B-cell lymphomas. (Kimball's Biology Pages, 2011)

As you can see in illustration 4, chromosome 18, containing the *BCL-2* locus, has undergone a reciprocal translocation with respect to chromosome 14, this contains the antibody heavy chain locus. This t(14;18) translocation places the *BCL-2* gene close to the heavy chain gene enhancer, which is very active in B-cells. => In t(14;18) cells, Bcl-2 protein is expressed at high levels cells.)

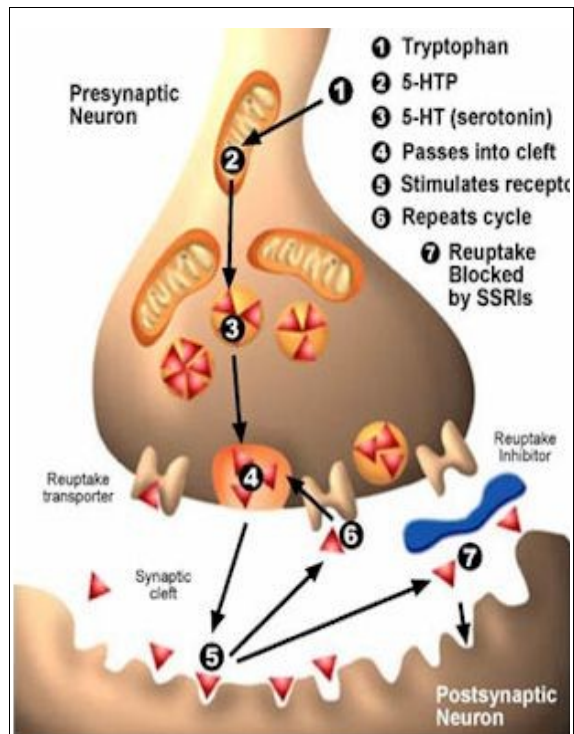


Illustration 3: Schematic illustration of 5-HTP conversion to Serotonin and mechanism of SSRIs. 1: Tryptophan enters system. 2: Converts to 5-HTP. 3: 5-HTP converts to 5-HT 4: 5-HT passes through membrane into synaptic cleft. 5: 5-HT stimulates its receptor. 6: 5-HT joins with the reuptake transporter to cycle through again. 7: Reuptake inhibitors (such as Prozac) increase 5-HT level in synaptic cleft by inhibiting the reuptake of 5-HT by the presynaptic neuron.

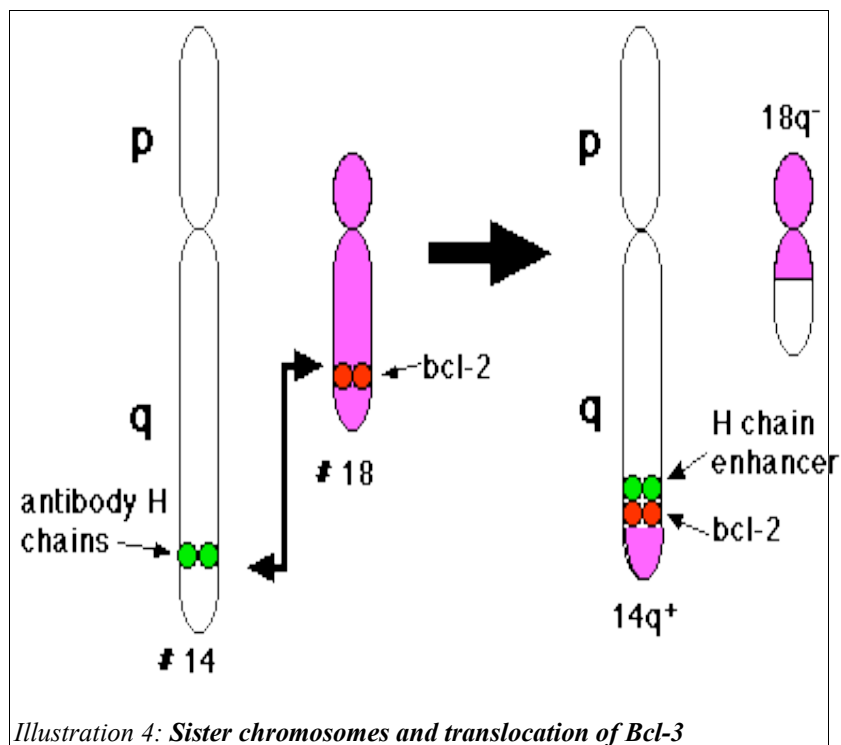
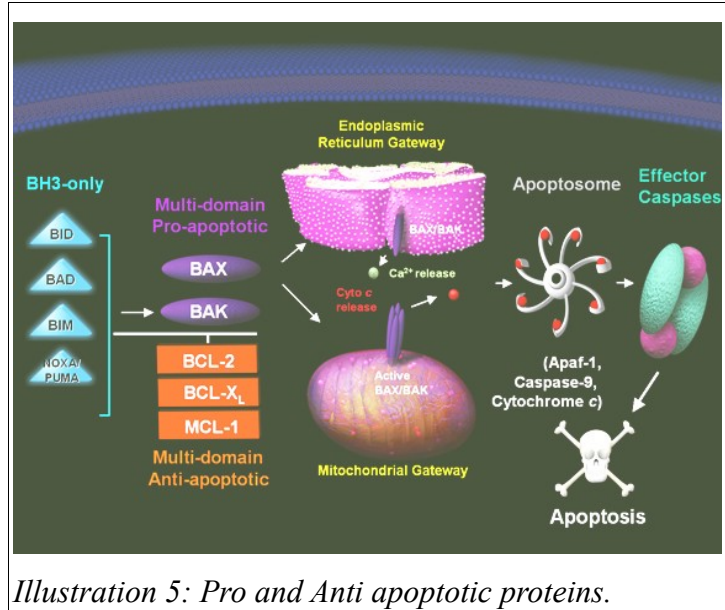


Illustration 4: Sister chromosomes and translocation of Bcl-3

There are two major categories of Bcl-2 proteins. Anti-apoptotic Bcl-2 proteins and Pro-apoptotic Bcl-2 proteins. The last have an important role in regulating apoptosis. Bcl-2 proteins control mitochondrial outer membrane permeabilization by activating the pro-apoptotic BCL-2 effector molecules, BAX and BAK (NCBI, 2000)(PNAS, 2008).



Blood Cells

In our bones we find the bone marrow, a soft substance responsible for the production of blood cells or stem cells, in their immature state. They will remain in the bone marrow till they become mature, being sent to the blood vessels by then. We named it peripheral blood. Bone marrow produces different kind of blood cells: white blood cells who fight infections, red blood cells to carry oxygen by tissues throughout our body and platelets to control bleeding.

Different types of blood cancer

Table 1:

Blood Cancers	Description	Treatment
Leukaemia	Affects Bone Marrow, destabilizes growth of white blood cells.	Chemotherapy, Immunotherapy, Radiation, Stem Cell Transplantation
Hodgkin's Lymphoma	Affects lymph nodes, accelerates cell production	Radiation, Chemotherapy, Stem Cell Transplantation
Non-Hodgkin's Lymphoma, Burkitt's Lymphoma	Affects lymphatic system, destabilizes lymphocyte, B-cell, T-cell.	Monitor Surveillance / Observation, Chemotherapy, Immunotherapy, Radiation, Stem Cell Transplantation,
Multiple Myeloma	Affects the plasma/white cells, leading to a abnormal growth of these.	Chemotherapy

Cancer Treatments

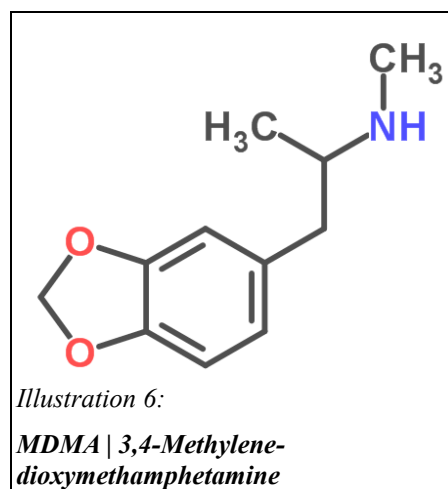
Table 2:

Treatments	Side effects
Chemotherapy	These depend on the type of pharmaceutical drugs and doses used. There is a higher chance of infection, hematomas or bleeding, tired and weak, loss of hair, a possibility in a colour change of the hair, nausea and vomit, diarrhoea and wounds in the throat and mouth.
Immunotherapy	Depends on the type of substances and the effect on the patient. Usually there is a swallow around the injection wound and some patients may present flu symptoms.
Radiation	Weakness and tired, a permanent probability of skin colour change, hair loss, nausea and vomit, diarrhoea.
Stem cells transplantation	If the stem cells received from a donor are rejected, these stem cells will attack the system of the one receiving them, affecting the liver, skin or the digestive system. It can be a serious problem, even fatal.
Monitoring Vigilance	There is no side effects on this type of treatments as in Monitoring there isn't much to be done then just waiting for the type of cancer to diminish by itself or the symptoms become more expressed.
Surgery	Surgery can end in a scar or if really unlucky, the operation can go wrong. But surgery is considered as a 100% treatment so side effects are non-existent, as in Monitoring vigilance.

MDMA

It is known as a party drug, also called ecstasy or M, taken mostly orally as pills or crystals which makes you have a happy feeling and lose your inhibitions. Which can let you go on the whole night in a high gear (Erowid, 2011).

It has also in been used for therapy against post-traumatic stress. It was created as a trial for antidepressants. MDMA is neurotoxic. It enters the axon terminals for serotonin, by the reuptake transporters, because MDMA has a bigger affinity



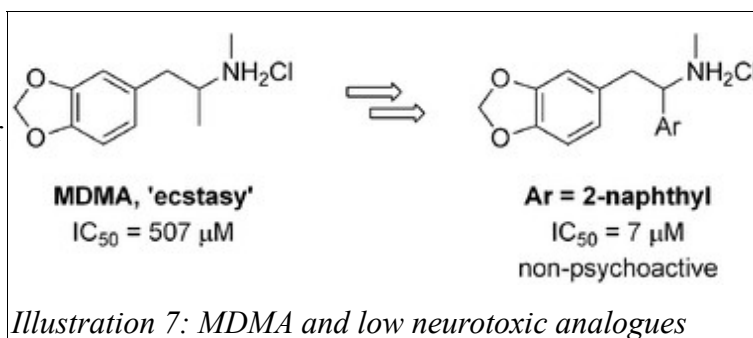
for the transporter than serotonin. Then it stimulates vesicles inside the axon to release a large amount of serotonin into the synapse. When such a large amount of serotonin is released into the synapse, it activates the serotonin transporters at the dendrite, which sends out the signal from the neurotransmitter to the rest of the brain and body. After a while MDMA will have caused all serotonin be released, and the body makes new serotonin slowly, this will cause a down effect. Then the re-uptake transporters will be exposed and dopamine can get up the serotonin axon. When dopamine enters the axon, it will be degenerated by MAO (Monoamine oxidase) which will cause oxidative stress because the free radical hydrogenperoxide is released, this will over time destroy the axons cells.

Possibly MDMA also cause an increase in neural activity, which uses more ATP than the mitochondria can create, this leads to cell death. Some of the side effects from MDMA can be wide, confusion, sleep problems, depression, bigger anxiety to smaller side effects as muscle tension, nausea, blurred vision, chills and excessive sweating. The effect MDMA gives when you take it, gets less intense the more regular you take it. And if you take it on a regular basis, the side effects can escalate to lesser performance and affect the short term memory. High doses of MDMA can potentially lead to interfere with the body's ability to regulate it's temperature which can cause hypothermia. Even though you don't get physical addicted to MDMA, you can still experience a form of withdrawal, fatigue, loss of appetite, depressive feelings and have trouble concentrating, if you stop using after a regular basis (thegooddrugsguide, 2011).

Researches have shown that extension of the α -substituent of MDMA larger than an ethyl group, made the psycho activity no longer exist. A reaction was made of different nitriles and piperonylzinc phosphate, that gave a series of piperonyl ketones. Which should be α -substituents (the first carbon attaching the functional group). (J. Gordon, 2010)

MDMA analogues

In research (J. Gordon et al., 2010) is being noted that lymphoma cells are targets for neurotransmitters. The serotonin transporter and the dopamine transporter that are not only located on the brain



cells but also they are located on the immune cells.

The fat in some of the blood cancer cell walls attracted MDMA, which then will cause serotonin to release in the cancer cells. The serotonin will stimulate the BCL-2 protein, and activate caspases, which will lead the BL cells to go into apoptosis (Healthland, 2011). The lymphoma cells that are being studied by Gordon et al. derive

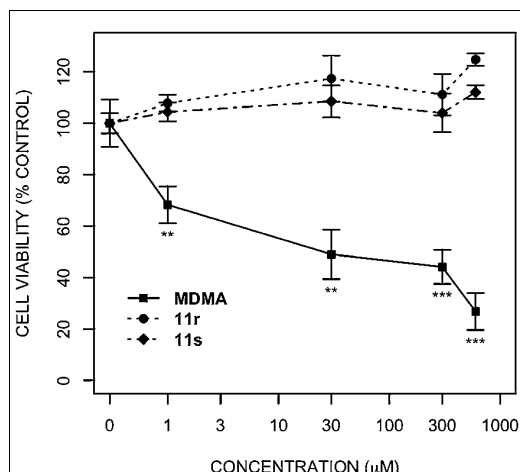


Illustration 8: Neurotoxicity MDMA compared to analogue 11r & s on cells ((cell line) SH-SY5Y)

from the immune cells called B-cells. B-cells make up to 80-90% of non-Hodgkin's lymphoma cases. When MDMA analogues were modified, a less toxic dose could be a good anticancer strategy according to the research.

Researches have shown that extension of the α -substituent of MDMA, larger than an ethyl-group, made the psych activity no longer existent. It was also found that attaching a phenyl-group increased potency against

sensitive Bcl-2 deplete, Burkitt's lymphoma cells 10-fold relative to MDMA. Also some related analogues were synthesized by containing 1-and 2-naphthyl and para-biphenyl substituents although they were 100-fold more potent. As well it can be seen in illustration 8 (J. Gordon, 2010) that the analogues are hardly toxic to the cells, while MDMA seems to be toxic, and is even noticeable at low doses.

Analysis

The treatments for cancer that exist nowadays have some heavy side effects that might be avoided by the research of a new treatment by using MDMA analogues. Of course, it cannot be available yet as the doses for this treatment remain unknown in order for the human body to resist the toxicity levels.

Table 3:

Chemotherapy VS MDMA analogues	
Chemotherapy side effects	MDMA analogues side effects (Known till now.)
Higher chance of infection, hematomas or bleeding, tired and weak, loss of hair, a possibility in hair colour change, nausea and vomit, diarrhoea and wounds in the throat and mouth.	Doses to treatment success are too high to be applied to human patients. It can treat the cancer but it might kill the patient if the doses are too high in a result of increasing the toxicity levels in the body.

So comparing these two treatments, the common drugs that are being used in Chemotherapy, nowadays to treat cancer, have many side effects. On the other hand, MDMA analogues' side effects might be much less, but it still is a substance under research. By our research, MDMA analogues can be a possible "candidate" for cancer treatment but in a few decades away.

Discussion

The treatments for cancer that exist nowadays have some heavy side effects that might be avoided by the research of a new treatment by using MDMA analogues.

There might even not be a side effect by using MDMA analogues. But first of all more tests needs to be made, to get an analogue which is not neurotoxic or causes psychoactivity but cytotoxic enough to cause the BL-cells to go into apoptosis and thereby kill the cancer.

The study leads in a direction of a better cancer treatment, with no heavy side effects, which also has the possibility of a much larger treatment rate.

For now the most successful tests has been on Burkitt's lymphoma, but the MDMA analogue has possibilities on most blood cancers, so there might be analogues that could be a better treatment for Leukaemia.

Conclusion

The studies gave us a link between MDMA and cancer. As for how it can be used as a treatment for cancer. The scientific studies showed that analogues which nearly ruled out psychoactivity could be made.

Those analogues that nearly ruled out psychoactivity did also increase toxicity towards killing the cancer cells. But there is still needed a larger amount of the analogue to kill the cancer cell, which results in the analogue still being neurotoxic. A more cytotoxic and less neurotoxic analogue, would be a promising new substitute for chemotherapy in cancer treatment. The side effects will be fewer than with chemotherapy, because the cancer cell attracts the MDMA. That makes MDMA more specific, which will rule out the same side effects that chemotherapy has, like cell death of nearby and fast dividing cells, which for example can cause hair loss.

Perspective

Further research should be done, to reach a more conclusive answer to whether MDMA-analogues can be applicable in cancer treatments. There is a long way to go, but it seems there a good possibilities. The analogues do kill cancer cells in the lab, so next steps could include research in small mammals, primates, and eventually clinical tests on humans, but that is a thing far off for now.

With further research, MDMA analogues might be a good substitute for chemotherapy for selected blood cancers.

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