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THE DIFFERENCES BETWEEN TYPICAL AND ATYPICAL ANTIPSYCHOTICS: THE EFFECTS ON NEUROGENESIS

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SUMMARY

Recently, the pharmacological division between typical and atypical antipsychotics has been called into question. New evidence, however, continues to emerge showing differences between these two classes of drugs. Hence typical and atypical antipsychotics are clearly different classes of drugs, as evidenced by their actions, mechanisms, effects and side effects. The most recently investigated field in which both classes of drugs have opposing effects is neuron survival and neurogenesis. Schizophrenia has been found to be a disease of progressive reductions in grey matter, and the more lost, the worse the outcome. Medication naïve patients have lowered levels of neurotrophins e.g. NT-3, NGF BDNF. The antipsychotic drugs alter the levels of these neurotrophins. Haloperidol, of the typical antipsychotics, causes neuron apoptosis by a free radical induced mechanism, involving Bcl-XS, P53, cytochrome c translocation and caspase 3 activation. Haloperidol also lowers BDNF levels, reducing neuroprotection in the brain to enable haloperidol's toxic effects. Atypical drugs have opposing effects. They increase levels of BDNF, improve cell survival and enhance neurogenesis. Atypical drugs can also prevent or reverse the effects of haloperidol induced toxicity. The mechanism involves the inverse agonism of 5HT receptors, particulary those of the 2A subset, but the situation is considerably more complicated.

Key words: *typical antipsychotics - atypical antipsychotics – schizophrenia – neurogenesis – apoptosis - 5HT2A receptor - D2 receptor*

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INTRODUCTION

Antipsychotics have been classified into two separate classes: typical and atypical. This distinction was originally made by the pharmaceutical companies while they sought to promote sales of the newly developed atypical drugs. Recently, it was argued that this dichotomy should be abolished (Cunningham Owens 2011). The evidence provided to support this opinion claimed that there was no difference in efficacy between typical and atypical drugs.

However, when we considered the studies originally used as evidence for a class abolishment, difficulties with this evidence became apparent. Measuring the efficacy of antipsychotic drugs is haphazard. Different studies use different measures of efficacy, ranging from discontinuation rates to patient opinion (Agius 2010). Thus, making cross-study comparisons is difficult at best. Therefore, taken as a collection of studies, the data is not conclusive in any meaningful way. We do not know which class is better and, more importantly, we cannot be certain that both classes have equal efficacy.

Even if efficacy is debatable, mechanism of action is much clearer cut. We know that typical drugs are D2 antagonists. We know that atypical drugs are 5HT receptor inverse agonists, but with actions on many other receptors. Furthermore, the differences in the side effects induced by the two classes cannot be ignored or understated. Typical drugs cause dyskinesias, including tardive dyskinesia. These are thought to arise from disruption to dopamine transmission in the basal ganglia. Atypical drugs have metabolic side effects. Although the exact consequence varies in degree from drug to drug, for example olanzapine may cause excessive weight gain-but not with all patients-, while many atypicals cause diabetogenesis.

However, as more studies are carried out, we see that typical and atypical antipsychotics are diverging and not converging, making the abolishment of the dichotomy ever more unlikely. New evidence has come to light recently, revealing that each class of drugs has a different effect on neurogenesis. Those who argue for the dichotomy suddenly have another pillar upon which to lay their argument: mechanism, action, side effects and now neurogenesis. The following paper is a review of the evidence, discussing how antipsychotics affect neurogenesis.

SCHIZOPHRENIA IS A DISEASE INVOLVING THE PROGRESSIVE LOSS OF GREY MATTER

To set it all in context, it is worthwhile reviewing the new evidence concerning schizophrenia. In schizophrenia, there is a reduction in the grey matter of the brain. This has been proven with MRIs (Lieberman et al. 2005). The loss of grey matter occurs in the frontal cortex, and results in an expansion of the lateral and third ventricles. The loss has been localised to the deep part of layer 3 of the dorsolateral prefrontal cortex (Glantz & Lewis 2000). Dendrite length is reduced by 50%. Spine density is lowered and there are fewer glial

cells. The dorsolateral prefrontal cortex is involved in attention. Hence, a loss of synaptic circuitry in that area may be a cause of attentional defects. The evidence also suggests that glutaminergic inputs are altered in the forebrain. Hence, this abnormal wiring is more likely to be a cause of schizophrenia than a downstream effect.

Critically, the loss of grey matter is progressive during the course of the disease (Cahn et al. 2002). This correlates to an exacerbation in illness. There has also been some evidence to suggest some relation with the dose of antipsychotic medication. The more grey matter lost, the worse the illness, and the higher the dosage of drug used to treat it. Despite this, the outcome is often worse and patients appear medication resistant. New evidence is suggesting that medication resistance may not be the reason behind a worse outcome; i.e. it may be iatrogenic or drug induced.

Nonetheless, if we accept the premise that loss of grey matter is the cause of schizophrenia, what remains to be investigated is how and why. Studies with neurotrophins have provided us with another piece of the puzzle. Neurotrophins have roles in neurogenesis, synaptogenesis, neuroprotection and modulate neural responses to stimuli (Buckley 2007). If the balance of these factors is tampered with in some way, the downstream effect may be a loss of grey matter, especially if cell apoptosis exceeds cell proliferation. The evidence makes that theory possible because there is an abnormal expression of these factors in schizophrenia. Drug naïve patients have been found to have reduced plasma concentrations of Brain Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF) and Neurotrophin-3 (NT-3) (Buckley 2007). This could lead to potential markers for diease progression in schizophrenia and allow us to make earlier diagnoses. In the context of neurogenesis, this means that a drug must alter the balance of these neurotrophic factors to have an effect.

NEUROGENESIS OCCURS IN THE ADULT BRAIN

What has allowed scientists to carry out the following studies has been the discovery that neurogenesis occurs in the adult brain. Experiments on post-mortem brain tissue found that cells retained the ability to proliferate in the dentate gyrus of the hippocampus and the subventricular zone (Eriksson et al. 1998). In addition, since the tests were carried out on post-mortem tissue, it is clear that these parts of the brain can proliferate throughout the lifetime of an individual. Thus, experiments with antipsychotics have studied these loci in the brain to determine whether or not there is a neurogenic effect.

Accordingly, it then was discovered that psychotropic drugs do indeed cause changes in proliferation in the subventricular zone (Nasrallah 2007). This set the scene for a collection of studies which tried to elucidate which drugs did what and how they did it.

TYPICAL ANTIPSYCHOTICS CAUSE NEURON APOPTOSIS IN THE BRAIN

Haloperidol is the most extensively tested drug of the typical class. As a D2 antagonist, it appears to reduce positive symptoms, but has no effect on negative symptoms.

When it was found that haloperidol causes apoptosis in the brain, the implications were serious. If schizophrenia is exacerbated by the loss of grey matter, a drug which causes loss of grey matter cannot be a viable treatment option. And yet, the evidence is irrefutable. Haloperidol induces neuron apoptosis (Galili 2000) but the study was careful to note that it was not necrosis. Therefore, this implies that the drug is hijacking cellular mechanisms to kill cells rather than simply being a noxious substance in its own right. Of course, haloperidol is not restricted in its effects to one part of the brain. While it was originally thought that D2 antagonism and dopamine disruption in the substantia nigra was the cause of tardive dyskinesia, a new theory suggests that haloperidol is instead killing the cells of the substantia nigra to cause the parkinsonism-like effects.

THE MECHANISM OF HALOPERIDOL-INDUCED APOPTOSIS HAS BEEN EXTENSIVELY STUDIED

Many experiments have been carried out in an attempt to validate the mechanism of haloperidol induced apoptosis. Upon haloperidol application, there was an increase in the levels of reactive oxygen species (ROS) arising from mitochondria. It was a six-fold increase and the level of glutathione (GSH) declines too (Sagara 1998). What is not clear is the order in which this happens. Does haloperidol increase ROS levels, and then GSH levels fall as it is used up in free radical scavenging? Or, is it that GSH levels decline and it is that which allows the ROS concentration to increase? The application of vitamin E also protects cell against haloperidol (Post et al. 2002). More evidence for mitochondrial based actions came when it was found that haloperidol also exacerbates rotenone toxicity (Tan et al, 2007). Hence, we have evidence pointing to apoptosis through excess free radical induction.

What complicates the issue is that which occurs further downstream. Bax levels and P53 levels rise (Post et al. 2002) and the p38 mitogen activated kinase and c-Jun-NH(2) proteins are stimulated (Noh et al. 2002). So far, it is easy enough to reconcile the studies together. Assuming all the studies are valid, there is a possible mechanism of action. Free radicals cause DNA damage, leading to a rise in P53. Once P53 levels reach a critical threshold, the cell commits suicide. P53 acts as a transcription factor, causing Bax levels to rise and form a pore, allowing cytochrome c to translocate from mitochondria. This was further supported when it was discovered that Bcl-2 application reduced haloperidol

apoptosis (Lezoualc'h 1996) because Bcl-2 prevents the Bax pore from forming. Cytochrome c activates caspases that carry out the suicide. Caspase 3 is particularly activated (Ukai 2004). Any other protein activation is probably a downstream effect but could also represent a second cascade.

Other evidence appears to disagree initially. One experiment has shown that haloperidol acts through the sigma 2 receptor system, involving Bcl-XS (Ukai 2004). However, the end result is still cytochrome c translocation, which therefore requires an increase in Bax levels. Further investigation into Bcl-XS reveals that Bcl-2 counteracts its apoptotic effects. In addition, the sigma receptor system leads to the modulation of calcium influxes. Calcium activates enzymes like NOS that lead to an increase in free radicals and nitric oxide toxicity. Therefore, all the evidence can be reconciled, if somewhat tenuously, and the evidence points to a single cascade with multiple start points. It remains to be seen what these start points are.

The most important thing to understand is that haloperidol causes apoptosis of grey matter in the brain.

HALOPERIDOL AND NEUROGENESIS

Studies have shown that haloperidol has no obvious effect on neurogenesis (Nasrallah 2010, Wakade 2002). However, evidence suggests that haloperidol reduces the levels of NGF and choline acetyltransferase (Parikh, 2004.) Experiments looking at the ventral pallidum, using haloperidol, have shown that there is a reduced concentration of BDNF and TOH (Meredith 2004). Thus, administration of haloperidol appears to be inducing, at least for the neurotrophic part, similar physiological conditions to schizophrenia. The reduction in concentrations of choline acetyltransferase will undoubtedly affect acetylcholine transmission in the brain. Reductions in TOH levels will affect catecholamine transmission in the brain, causing disruptions in serotonin, dopamine and noradrenaline pathways.

Reduction in neurotrophins does not necessarily reduce neurogenesis. The studies mentioned above were only looking to find newly dividing neurons. However, neurotrophins do not just induce neurogenesis, they have many other roles. The decline in neurotrophins causes reduced neuroprotection, making cells more predisposed to apoptosis. Thus, with haloperidol, the balance is shifted: increased apoptosis and reduced neuroprotection against maintained neurogenesis. The overall result is a loss of grey matter without a change in neurogenesis.

The theories are further supported because D2 agonism reduces the effect of haloperidol (Ukai 2004). It is more likely that the reduction occurs because of competition between the agonist and haloperidol, rather than any downstream cascade from the D2 receptor. Applied BDNF reverses the toxic effect of haloperidol, proving that BDNF is neuroprotective. What is even more promising is that 5HT2A receptor blockade reduces haloperidol toxicity. Atypical antipsychotics block the 5HT2A receptor.

ATYPICAL DRUGS ENHANCE NEUROGENESIS AND COUNTERACT THE EFFECTS OF HALOPERIDOL

Atypical drugs act on the 5HT2A receptor. They are not antagonists but inverse agonists, in effect causing a reversed effect. They also act upon a range of other receptors, but the respective affinities vary from drug to drug. In sharp contrast to haloperidol, drugs like risperidone have a weak potential to cause injury to cells (Ukai 2004). These atypical drugs also cause neurogenesis (Wakade 2002).

Studies with clozapine have shown that pretreatment and post treatment reverse the effects of haloperidol toxicity (Parikh 2004). In addition, the drug can increase NGF plasma levels in medication naïve schizophrenia patients. The level of NGF is increased to approximately normal levels. Although this presents a possibility of using neurotrophins to treat schizophrenia, it is important to remember that while we can stimulate neurogenesis, we cannot ensure that the proper connections are made.

Atypical drugs have other effects that are in opposition to haloperidol, and these actions promote cells survival. Atypical drugs reduce caspase activation (Gasso 2012), block glutamate toxicity (Abekawa 2011) and ameliorate rotenone induced toxicity (Tan 2007), actions in direct contrast to those of haloperidol. In the latter study, it was also found that risperidone increases BDNF, c-fos and STAT-3 expression. All three of these molecules are cell survival factors and, coupled with rises in NGF, we can see that atypical drugs have a powerful neuroprotective effect.

MECHANISM OF NEUROGENESIS

Of course, in addition to cell survival, atypical drugs also have effects on neurogenesis. The effect is probably modulatory rather than stimulatory, but then the process of neurogenesis is still not totally clear. A range of studies have been carried out to elucidate the mechanism of atypical-induced neurogenesis.

Agonism of the 5HT2A receptor reduces the levels of BDNF. Hence, antagonism would block this decrease. Inverse agonism should increase the levels of BDNF and indeed, this is what happens (Vaidya 1997). In addition, stress activates the 5HT2A receptor. This is thought to be the mechanism behind the neurodegeneration in the hippocampus in depression.

Conversely, agonism of the 5HT2C receptor causes neurogenesis in the dentate gyrus and, in the subventricular zone, neurogenesis is stimulated by 5HT2A blockade (Banasr et al. 2004). Thus, we can assume that neurogenesis is modulated by a set of 5HT

receptors, with different receptors in different loci having different effects on modulation. In all of these, serotonin transmission is important. Serotonin increases levels of neurotrophins but neurotrophic factors can often be both stimulatory and inhibitory. Again, this can depend on the type of receptor being expressed for the neurotrophin. Thus, BDNF may reduce neurogenesis when acting on a receptor expressed in one locality, and do the reverse on a different receptor elsewhere. This theory allows us to make some sense of what can appear to be conflicting evidence. However, it also greatly complicates the mechanism of neurogenesis, and it may be many years before we are able to fully understand this mechanism.

CONCLUDING REMARKS

The data is very persuasive. While the mechanisms of action are still to be fully discovered, certainly it appears that typical and atypical antipsychotics have different mechanisms of action at the level of neurotrophins and neurogenesis. Haloperidol and atypical drugs have opposing effects on cell viability and neurogenesis. Hence they must remain in two separate classes.

The data also raises the possibility of other hypotheses. Haloperidol induces apoptosis in grey matter, which means that there is a chance that part of the disease progression in schizophrenia is iatrogenic. The glutamate block caused by both classes of drugs suggests that perhaps the dopamine theory of schizophrenia is too simplistic. It may be that any dopamine changes are caused by upstream effects involving changes in glutamate transmission. As a result, much of what we have believed to be true in the past may need to be reviewed.

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