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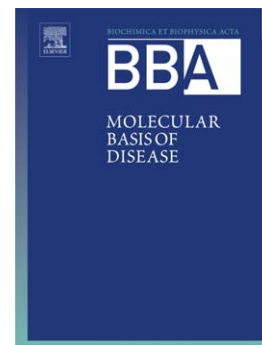
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The Cell Cycle Hypothesis of Alzheimer's Disease: Suggestions For Drug Development

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Summary

The cell cycle hypothesis of neural dysfunction in chronic neurodegenerative conditions such as Alzheimer's disease (AD) offers a unified approach to understanding both existing and novel strategies for drug development. At the present time, a ligand based approach is a pragmatic solution for identifying new chemical leads on which to base future discovery and optimisation. We have pursued a ligand based approach on the basis of public domain data to identify existing compounds capable of abrogating the cell cycle at the G₀-G₁ interface. Selected on this basis, irrespective of the tissue under study, we identified several classes of compounds as potential chemical leads. Of these compounds, at least ten have already been shown to be neuroprotective in animal models of acute neurodegeneration. Such compounds could form the basis of a screening exercise after development of suitable screening tools. Progressing of chemical leads through such an approach will be more efficient if future leads display relevant "drug-like" properties. Further, drug development in this arena should take account of the special concerns raised by targeting an elderly population. This will involve accounting for frequent polypharmacy in the aging population, and age-related alterations in physiology.

Introduction

Neurodegenerative diseases represent a significant and growing social and economic problem for the developed world. Of these, Alzheimer's disease (AD) perhaps best illustrates both the healthcare impact and potential for revenue generation within this sphere. The cost of care for patients with AD is \$150 billion [1]. The current market for AD therapeutics is \$3 billion annually, predicted to grow to \$7.9 billion in 2012 [1]

At present the following therapeutics are marketed for the treatment of AD - donepezil (Aricept™), rivastigmine (Exelon™), galantamine (Reminyl™) and memantine (Nemanda™). The first three of these are acetylcholinesterase inhibitors, the last a glutamate receptor antagonist. Unfortunately, these therapeutics provide only symptomatic relief, rather than targeting underlying disease mechanisms, i.e., they are not disease modifying. As such, despite current state of the art therapeutics, individuals with AD face inevitable declines in cognition. Therefore, it is not surprising that the impact of therapeutics targeting symptomatic relief in patients with AD has been questioned, particularly with respect to cost effectiveness [2], although current analysis may not have explored potential neuroprotective effects in patients [3].

The development of potential disease modifying therapeutics has frequently had a basis in targeting the deposition of amyloid- β known to occur in patients with AD [4]. However, as discussed elsewhere [5], the role played by amyloid- β in AD remains the subject of debate. On the other hand, the cell cycle hypothesis is a novel pathophysiological approach to neurodegeneration in AD [6-10]. This hypothesis has the virtue of suggesting a potential explanation for alterations in amyloid- β processing as well as other pathological derangements of neuronal metabolism [11]. For example, it is known that cell cycle dependent mechanisms regulate phosphorylation and metabolism of APP in neuronal-like tissues [12]. Another virtue of the cell cycle hypothesis of AD is the derivation of new potential therapeutic approaches. In this review, we focus on issues relating to drug development around the cell cycle hypothesis.

The Cell Cycle Hypothesis

The cell cycle hypothesis proposes that either mitogenic signalling, or cell cycle control, or both, are deranged with respect to neurons within the brain of individuals with AD [13, 14]. Therefore pharmacological intervention targeting mitogenic signalling or cell cycle control should act against the neurodegeneration seen in this condition. Further, since neurons engaged in a derangement of cell cycle function will be metabolically and functionally compromised, pharmacological reversal of this metabolic compromise may also provide symptomatic relief.

Of mitogenic signals in cell cycle-mediated neurodegeneration, some are well known and have been subject to drug development research for some time. For example, excitotoxicity and hypoxia are suggested mitogens, as are pro-inflammatory processes and elevations in growth factor release [14-16]. Therefore antagonists of glutamate excitotoxicity could be envisaged as decreasing mitogenic drive and cell cycle activation in AD brain. According to this, the symptomatic relief offered by the glutamate antagonist memantine [17] is in accord with the cell cycle hypothesis. Similarly, acetylcholinesterase inhibitors, known to be clinically active in AD patients, may have cell cycle-related activity, arresting mitosis in neuroblastoma cells [18]. However, approaches such as the excitotoxic hypothesis or theories based on inflammation of the CNS are capable of suggesting potential therapeutic approaches without recourse to the cell cycle hypothesis. Therefore, it is more of interest to focus on candidate therapeutics identified specifically by the cell cycle hypothesis that would not be identified by other approaches.

Neurons undergo cell cycle progression in AD, to the point that DNA replication occurs [19]. DNA replication presumably produces a gene dosage effect and, in this regard, it is notable that individuals with Down's Syndrome also suffer from a trisomy 21 gene dosage effect, and that all individuals with Down's Syndrome will develop AD-type clinical and pathological changes. Therefore, any approach tackling the metabolic consequences of DNA replication in AD may have some therapeutic utility. However, since drug development in this arena awaits further research, at the present time, there is no data available to delineate among the numerous potential targets defined by this approach.

Drug Development

According to the cell cycle hypothesis, neurons in AD have left quiescence and progressed from G_0 to the G_1 phase of the cell cycle. As such, a potential therapeutic approach would be to target aborting progression through the cell cycle at this early stage. A potential therapeutic capable of this approach would prevent neurons entering the S phase, and neurons treated in this way would not suffer either a gene dosage effect or subsequent neurodegeneration.

Attempts to trigger abrogation of the cell cycle at the G_0 - G_1 interface can be derived from two starting points. The first would rely on an understanding of the neuronal "cell cycle" and its relationship to the cell cycle in dividing tissues. A complete mapping of the neuronal cell cycle in this way would generate targets defined by molecular biology capable of forming the basis of drug discovery research. This level of understanding may not yet be complete.

A second route forward centres on taking a compound based approach, rather than focussing on molecular biological targets. This less elegant, but potentially more pragmatic strategy, would involve identifying compounds with a known ability to trigger reversion through the G_0 - G_1 "gate", and so prevent cell cycle progression, in other tissues. These compounds can then become "chemical leads" For the purposes of this discussion, "chemical leads" are defined as compounds forming a starting point for driving forward screening of potential therapeutics, having a desired pharmacological activity. Such compounds form the basis for future drug development, in that manipulating such a lead via synthetic medicinal chemistry may produce compounds with greater efficacy or an improved safety profile. Commonly within the pharmaceutical industry, chemical leads are New Chemical Entities. We are suggesting here that existing compounds may also function as chemical leads, and we have reviewed available data accordingly. The proposal here therefore is to screen known compounds that in many cases are already available in the clinic, primarily to inform development of novel medicines. A corollary benefit of this approach may be derived from the fact existing compounds would be screened. If clinically available compounds are identified as active, these may be used therapeutically as well functioning as the building blocks of

future medicines. In order for this dual utility to exist, any such compound would not only have activity in a cell cycle context, but would also have to meet the criteria for a therapeutic suitable for an aged population. Compounds identified by such an approach should have a variety of properties in order to have maximum utility in a population suffering from, or at risk for, AD. These are outlined in Table 1 and are discussed in further detail below.

One source of potential chemical leads is compounds that have previously been developed as anti-proliferatives or anti-tumour agents, or that otherwise are known to trigger cell cycle arrest at the G₀-G₁ transition. We have looked at compounds known to have this capability, reviewing anti-tumour agents as well as compounds acting at this point in the cell cycle in cells not derived from tumours. Defining potential chemical leads for screening in this way will aid development of novel therapeutics providing that such compounds are tolerable in an AD population. Such tolerability may not be demonstrated by older chemotherapeutics but is apparent in more modern molecularly targeted anti-proliferatives. An advantage of screening existing compounds is that such compounds will have a known clinical profile. Therefore their suitability for use in AD patients can be examined in light of both future screening in pre-clinical models of AD and their known tolerability in patients ,

An issue with some of these compounds relates to their intended function in oncology – namely induction of apoptosis and therefore the destruction of tumours. Clearly, whilst induction of cell death is an advantage for cancer patients, such an effect is not desirable in AD. It is therefore of importance to examine the known data on the effects of these compounds as neuroprotectives. Since currently there are no ongoing programmes looking for effects of such compounds in chronic neurodegenerative processes, we have looked at *in vivo* models of acute neurodegeneration as the most sophisticated benchmark available.

Table 2 lists compounds which are known to trigger cell cycle arrest at the G₀-G₁ transition. These compounds come from a wide range of chemical and pharmacological classes, as diverse as flavopiridol [20], retinoic acid [21] and PD098059 [22]. The effects of these compounds in relatively sophisticated models of acute neurodegeneration, in at least ten cases, suggest protection

against acute neurodegeneration. This suggests that anti-proliferative and anti-tumour compounds with the ability to cause cell cycle arrest at an early stage have a broad based neuroprotective efficacy, and that identification of chemical leads on the basis of identification of G₀-G₁ arrest ability in many tissues is a viable approach. Another point of interest is that, alongside memantine and at least one acetylcholinesterase inhibitor, several compounds having potential utility in AD have effects on aborting the cell cycle. For example, the anti-diabetic PPAR gamma agonist glitazones Rosiglitazone and pioglitazone [23, 24] may have utility in AD. Such compounds cause G₀-G₁ cell cycle arrest [25]. Similarly, the use of statins has been reported to impact development of AD [26], and several statins are known to arrest the cell cycle at G₀-G₁ [27, 28].

Further investigation of potential chemical leads should consider the potential of the compounds under consideration for such issues as brain penetration, suitability for chronic administration, and optimal routes of metabolism. Brain penetration can be estimated to some degree by computing or measuring the variable log P, since existing information allows a prediction of likely brain penetration based on this value. Many chemotherapeutics and anti-proliferatives have adverse side effects that are acceptable during acute use in oncology, but would be unacceptable for use in prophylaxis or treatment of AD. Finally, using a compound that is metabolised specifically by one hepatic enzyme increases risk in development and should be avoided.

Identification of potential chemical leads according to the criteria above should provide tools for investigation and screening in relevant in vitro and in vivo assay systems. Such screening methodologies are currently being developed [29]. Once identified, compounds meeting criteria may be used in clinical tests of the cell cycle hypothesis. Such clinical investigation should take account of issues related to drug development in elderly populations. Some of these issues are discussed below.

Drug Development in the Elderly

In recent years there has been an acceptance that “adult humans” are not a single, homogenous entity. Not only do the sexes vary in CNS disease pathology, but differing age groups cannot be

considered equivalent. It is now widely recognised that paediatric patients cannot be regarded as “small adults” with regard to drug therapy. Any approach suggesting that paediatric patients can be administered pharmaceuticals on the basis of dose proportionality according to weight is potentially flawed. Therefore, the FDA, for example, has for some years sought to incentivise targeted paediatric drug development [30]. By analogy, development of potential therapeutics for populations of the age range at risk for the development of AD cannot be entirely driven by assessments based on research on healthy young adults. Populations over the age of sixty five differ from younger populations in crucial ways.

The aging body will respond to medical intervention differently from the young body. Additionally, the elderly patient population will differ from the younger population in terms of concomitant medication usage – Table 3 gives an indication of the range and prevalence of concomitant medication usage in the elderly. The elderly patient is at risk from falls and injury associated with use of brain penetrant medication [31], in a way not seen in younger patients. Potential problems occur with drug interactions (DIs) and adverse drug reactions (ADRs) in certain sub-populations unidentified through trials. Drug interactions are a major issue for the drug development process. This is especially true for elderly populations due to polypharmacy (about 80% of the elderly are on more than one medication concurrently [32, 33] and changes to pharmacokinetics (body's procedural responses) and pharmacodynamics (affective responses) based on shifts in disease and physiology.

Drug pharmacokinetics differ in the elderly. Pharmacokinetics describes four components which have differing importance in terms of drug application and interaction: absorption, distribution, metabolism and elimination.

Diseases and ageing can compromise gastro-intestinal absorption. The loop diuretic furosemide, for example, has much lower efficacy due to poor absorption in elderly patients who have suffered from heart failure [34, 35]. Drug-drug interactions (for example between certain drugs and some antacids) can also prevent successful absorption.

Distribution problems can occur in the elderly due to the tendency for lower total body water, lower muscle mass and increased body fat relative to normal adults, leaving serum concentrations less predictable as a result of irregular volumes of distribution. Interactions in distribution can occur due to competitive binding for transport. For example, NSAIDs have a tendency to displace other drug molecules from protein binding [32].

Drug metabolism depends upon a family of hepatic enzymes: the cytochrome p450s. Some drugs are known to induce or inhibit some of these enzymes, either ones involved in their own biotransformation or not, particularly in drugs with long half-lives. In cases of polypharmacy (especially in the elderly) this leads to unpredictable volumes of distribution and potential dosage problems. Care must therefore be taken in prescription so that ADRs and dangerous drug interactions do not occur.

Some drugs are excreted through renal elimination. Interference with renal excretion may therefore result in toxic levels of drugs. Interactions can occur when urinary pH is altered by administering ascorbic acid (or other acidifying drugs) or antacids (or other alkalizing drugs). Other interactions can occur in the kidneys through competition in the active transport mechanisms of the kidneys. Examples include probenecid co-administered with antibiotics and quinidine in conjunction with digoxin [32].

Using the appropriate in vitro assays while carrying out pre-clinical trials helps the drug development process. Testing for CYP induction and inhibition, metabolic stability, plasma protein binding, drug-drug interactions etc. could provide essential safety information ahead of clinical trials. It is important that this information is treated with care though, and not used to extrapolate blindly into human application in phase I trials.

Pharmacodynamics of the elderly also poses a problem to drug development. Changes to receptor affinity, post-receptor events and homeostatic control occur in ageing. Studies of specific volatile

pharmacodynamics in the elderly have been done with benzodiazepines and verapamil. Toxicity in some cases may be as a result of pharmacodynamic changes. Interactions can transpire due to these changes, due to tissue responses and receptor binding etc. Not much is known about which changes occur and where, but it will depend on the individual and is part of the ageing process, which must be considered in drug development.

Other issues in drug development are more general. One such issue is that elderly people need to be used in clinical trials. Sometimes in the past, clinical trials have neglected the elderly due to access, concerns about polypharmacy and adverse reactions, but at least a subset of elderly participants should be used in every trial of a medication that will be used by the geriatric population. This would at least clarify where each new drug has adverse effects and may even allow information to be extracted about its interactions as well as seeing where it would fit in with dosing regimens. At the moment, if elderly patients are used in clinical trials, it tends to be the “young” elderly and thus caution should be taken in translating this to older patients where the treatments are most likely to be required.

Drug formulation can also be an issue. Due to the physical and cognitive challenges of the elderly, the doses, containers, pills etc. may not be appropriate and setbacks occur. So long as patients are monitored, dosages and other problems can be adjusted, but it is important to be aware of these issues

Conclusions

The cell cycle hypothesis of AD has generated new ideas, and questions the utility of targeting amyloid- β deposition from a therapeutic point of view, in distinction to addressing the cause of altered amyloid- β processing in this disease. At the same time, the hypothesis generates exciting new possibilities for development of novel therapeutics.

Our current understanding of processes underlying the neuronal “cell cycle” is potentially not sufficiently advanced to create molecular biological targets for the development of novel

therapeutics. However, a pragmatic ligand centered pharmacological approach already suggest that identifying existing compounds capable of arresting abnormal entry into the cell cycle will yield new neuroprotective agents. Thus far, data have been generated in animal models of acute neurodegeneration. Alongside this data, compounds known to have potential clinical utility in AD can also be shown to mediate exit from the cell cycle. There is therefore precedent supporting drug discovery efforts based on such an approach. Such discovery will rely on the development of relevant screening tools.

Using such a process to identify chemical leads will be enhanced if such chemical leads have suitable properties for use in the clinic. That is, optimisation of chemical leads tends to compromise general "drug like" properties of molecules, and therefore an ideal chemical lead will present an acceptable profile at the outset. Early consideration of potential for brain penetration, avoidance of metabolic interactions and side effects or toxicity on chronic administration is required, alongside recognition of the special problems of drug development in elderly populations.

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Table 1: Desirable properties of chemical leads used in drug discovery research targeting the cell cycle basis of Alzheimer's disease.

Property	Relates to:
Abrogates cell cycle at G ₀ -G ₁ stage	Efficacy
Log P = 2 ± 0.7	Favours brain penetration
Log P ~ 2	Favours oral Absorption
Log P < 4	Avoids distribution into fatty tissue
Metabolism - If hepatic polyzymic	Less variable pharmacokinetics
Absence cytochrome p450 inhibition or induction	Reduced drug – drug interaction
Lack of sedative or motor effects	Side effects

Table 2: Known drugs that arrest cell cycle progression at the G₀-G₁ stage – acute neuroprotection

Compound	Action	Neuroprotective	Reference
Retinoic Acid (Vitamin A)	G ₀ -G ₁ cell cycle arrest and expression of G ₀ proteins: p62 and p56	Active in rat model stroke	[36-39]
Calcitriol (Vitamin D)	G ₀ -G ₁ cell cycle arrest and other cycle regulatory procedures	Active in rat stroke model	[40-42]
Flavopiridol	Ras-MAPK-Apt and cyclin D1, G ₀ -G ₁ cell cycle arrest	Active in rat model of TBI	[20, 43]
Glucocorticoids	Dexamethasone enhances vitamin D response, G ₀ -G ₁ cell cycle arrest	Active in rat model TBI	[40, 44, 45]
Interferon-alpha	G ₀ -G ₁ arrest	ND	[46]
PD 0332991	G ₁ cell cycle arrest via cdk 4/6 inhibition	ND	[47, 48]
Inositol hexaphosphate (IP6)	G ₀ -G ₁ cell cycle arrest	ND	[49]
N6-isopentenyladenosine	G ₀ -G ₁ cell cycle arrest via inhibiting farnesyl diphosphate synthase	ND	[50]
Simvastatin	G ₀ /G ₁ cell cycle arrest	Active in rat stroke model	[27, 51]
Taurine	G ₀ /G ₁ cell cycle arrest	Active in rat stroke model	[52, 53]
TGF-beta-1	G ₀ -G ₁ cell cycle arrest via induces cdk inhibitors cip/kip and INK4 family	Active in mouse stroke model	[21]
Interleukin-1	G ₀ -G ₁ cell cycle arrest	ND	[54]
Farnesyltransferase inhibitors	G ₀ -G ₁ cell cycle arrest via Ras regulation	ND	[55]
U0126, PD098059	G ₀ /G ₁ arrest through RAS - MEK - ERK inhibition	Active in TBI model	[22]
Sphingosine and ceramide	G ₀ /G ₁ cell cycle arrest via Rb dephosphorylation	Active in rat stroke model	[56, 57]
L-796,449, Rosiglitazone	G ₀ -G ₁ cell cycle arrest via PPAR gamma agonism	Active in rat stroke model	[25, 58-60]
SJ749	G ₀ /G ₁ cell cycle arrest, alpha5beta1 integrin antagonist	ND	[61]

Table 3: Most commonly prescribed therapeutics to the elderly population

Drug	Description	Annual Prescriptions (millions)
Lipitor	Statin	63.2
Hydrochlorothiazide	Diuretic	42.8
Atenolol	Beta blocker	42.0
Furosemide	Loop diuretic	34.8
Norvasc	Calcium channel blocker	32.6
Synthroid	Hypothyroidism	30.7
Zoloft	Anti-depressant	27.0
Nexium	Proton pump inhibitor	22.9
Zocor	Statin	22.4
Prevacid	Proton pump inhibitor	22.2
Metoprolol Tartrate	Beta Blocker	22.0
Plavix	Anti-platelet	18.8
Fosamax	Biphosphonate	17.9
Protonix	Proton pump inhibitor	16.4
Toprol XL	Beta blocker	16.4
Klor-Con	Electrolyte replenisher	11.4
Celebrex	NSAID	11.0
Actonel	Biphosphonate	9.7
Prilosec	Proton pump inhibitor	7.4
Xalatan	Prostaglandin	6.9
Aricept	Acetylcholinesterase inhibitor	4.3
Lanoxin	Digoxin	3.5