



Review

CNS-active drugs in aging population at high risk of cerebrovascular events: Evidence from preclinical and clinical studies

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Abstract

The recovery process following cerebral insults such as stroke is affected by aging and pharmacotherapy. The use of medication including CNS-active drugs has increased in the elderly during recent years. However, surprisingly little is known about how safe they are with respect to severity of sensorimotor and cognitive impairments or recovery of function following possible cerebrovascular accidents. This review examines the experimental and clinical literature, primarily from 1995 onwards, concerning medication in relation to cerebrovascular events and functional recovery. Special attention is directed to polypharmacy and to new CNS-active drugs, which the elderly are already taking or are prescribed to treat emerging, stroke-induced psychiatric symptoms. The neurobiological mechanisms affected by these drugs are discussed.

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Keywords: Aging; Cognitive functions; Cerebrovascular events; Functional recovery; Medication; Sensorimotor impairment

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Abbreviations: AD, Alzheimer's disease; BDNF, Brain derived neurotrophic factor; BrdU, Bromodeoxyuridine; CNS, Central nervous system; CIT, Constraint-induced therapy; CREB, cAMP response element-binding protein; ECT, Electroconvulsive therapy; fMRI, Functional magnetic resonance imaging; GABA, Gamma-aminobutyric acid; GAP-43, Growth-associated protein-43; LTD, Long-term depression; LTP, Long-term potentiation; MCAO, Middle cerebral artery occlusion; MAO-B, Monoamino oxidase B; NMDA, N-methyl-D-aspartate; PET, Positron emission tomography; SSRI, Selective serotonin reuptake inhibitors; SVZ, Subventricular zone; TMS, Transcranial magnetic stimulation; TIA, Transient ischemic attack

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1. Introduction

While a decrease in risk factors and improved diagnosis and medical management have contributed to a marked decline in the incidence of stroke, it remains the third leading cause of death in the industrialized world, surpassed only by heart disease and cancer, and is a leading cause of disability in adults (Ingall, 2004; Kelly-Hayes, 2004). Only a few acute stroke patients can be treated with thrombolysis within 3 h of symptom onset (Markus, 2005). Thus, effective and safe treatments to prevent or restrict the acute neuronal damage occurring after stroke are needed. Interestingly, nearly all stroke patients show various degrees of spontaneous functional recovery from their initial impaired state (Arboix et al., 2003; Nakayama et al., 1994). So far, rehabilitation has been regarded as the only possibility to enhance patients' capabilities after stroke. A better understanding of brain restorative mechanisms after stroke is expected to lead to novel therapies directed at improving functional outcome.

Both experimental and human studies suggest that the age of the individual has an important impact on functional recovery after brain damage, although the data are conflicting (Popa-Wagner et al., 1999; Zhang et al., 2005a). Brain physiology and neurochemistry change during aging and as a consequence the neurobiological response to brain insults may be altered. In addition, experimental studies have shown that certain classes of drugs affecting specific neurotransmitter systems can influence both the rate and degree of functional recovery after brain injury (Feeney et al., 1982, 2004). Clinical studies have shown that the same drugs examined in rodent studies (e.g., amphetamine, clonidine, prazosin, dopamine receptor antagonists, benzodiazepines, phenytoin) often have a similar impact in humans recovering from stroke, but not always (Crisostomo et al., 1988; Goldstein, 1995, 1998; Walker-Batson et al., 1995).

It is very common that stroke patients are prescribed antipsychotics, antidepressants, cholinesterase inhibitors, and sedatives for the treatment of agitation, insomnia, cognitive dysfunction, mood decline, anxiety and other complications and coincident disorders (Berthier et al., 2003; Eriksson et al., 2004; Erkinjuntti et al., 2004; Leker and Neufeld, 2003). More importantly, an increasing number of new psychotropic medicines are being prescribed without an understanding of their effects on possible cerebrovascular events or functional recovery

after a stroke. In this review, we describe the effects of aging and new central nervous system (CNS)-active medication on functional recovery following stroke.

2. Medication, aging and stroke

The number of elderly people will increase dramatically in upcoming years. Whether or not they sustain a cerebrovascular insult, a large number will have clinical signs of mood disorder, psychosis, dementia, anxiety, and sleep problems. Many of them will be taking one or more drugs that act in the CNS, such as antidepressants, antipsychotics, cognitive enhancers, and hypnotics, for the purpose of primary care and treatment of behavioral disturbances related to aging (Elmstahl et al., 1998; Hartikainen et al., 2003a; Lasser and Sunderland, 1998; Linjakumpu et al., 2002a). On a global basis the elderly use psychotropics more frequently than the general population, and this increases incrementally over the life span, except perhaps in the very oldest age groups (Blazer et al., 2000; Hartikainen and Klaukka, 2004; Ohayon et al., 1998). Finnish studies have revealed that both men and women aged 75 years or over use anxiolytics, sleeping pills, antipsychotics, and antidepressants more commonly than other age groups (Hartikainen and Klaukka, 2004; Hartikainen et al., 2003b).

It has been reported that 20–53% of nursing home residents are taking antipsychotic medication, including atypical antipsychotics such as risperidone, in order to control delusions, aggression, and anxiety related to dementia (Lasser and Sunderland, 1998; Ruths et al., 2001; Sorensen et al., 2001). The use of antidepressants is also common, from 11% to 20%, among home-dwelling elderly individuals; and in institutional care the use is even more prevalent, up to 61% (Hartikainen et al., 2003a, b; Lasser and Sunderland, 1998; Ruths et al., 2001; Skoog et al., 1993; Sorensen et al., 2001). Selective serotonin reuptake inhibitors (SSRI) like fluoxetine are the most commonly used antidepressants (Hartikainen et al., 2003a, b). Use of antidepressants, including tricyclic preparations and SSRIs, is associated with falls or fractures (Ensrud et al., 2003; Kallin et al., 2004; Lawlor et al., 2003; Liu et al., 1998a). The risk is dose dependent and is maintained with long-term use (Thapa et al., 1998).

Polypharmacy is common in the elderly (Elmstahl et al., 1998; Linjakumpu et al., 2002a, b; Weiner et al., 1998).

The use of two or more CNS-active drugs at the same time is related to an increased risk of falls and fractures compared to the use of one drug alone (Weiner et al., 1998), although it is unclear whether the risk is caused directly by the drugs. In patients with Alzheimer's disease, use of antipsychotics and sedatives is associated with a higher risk of deterioration, particularly when used together (Ellul et al., 2007). In general, polypharmacy increases the possibility of unexpected interactions and adverse effects, which may be exaggerated with aging due to changes in pharmacokinetics and pharmacodynamics, and a decline in neuronal number and function (Barat et al., 2000; Hughes, 1998; Pollock, 1998; Tune et al., 1992). Changes in body composition due to aging cause pharmacokinetic alterations in absorption, distribution, and elimination via metabolism in the liver and/or in excretion by the kidneys; and the half-life of fat-soluble medicines multiply. For example, the half-life of diazepam can be delayed from 20–48 to 90 h in persons aged over 80 years (Cummings and Le Couteur, 2003). The pharmacodynamic responses of benzodiazepines also tend to change with advancing age; the concentration that produces half of a full response (EC₅₀) for sedation is reduced by 50% in elderly persons.

Frequently the mechanisms of action among drugs given to the elderly are conflicting, which may have implications for people who will have, or have had, a brain injury and who take more than one psychoactive drug at one time. For example, new generation atypical antipsychotics have serotonin antagonist properties whereas, in contrast, the most commonly used antidepressants are indirect serotonergic agonists. Does treating a patient with an antipsychotic drug for agitation degrade the ability to treat that same patient with an antidepressant for depression? Atypical antipsychotic drugs also are cholinergic antagonists (Raedler et al., 2000), whereas most cognitive enhancers are cholinesterase inhibitors which increase synaptic acetylcholine. Surprisingly, atypical antipsychotic drugs increase acetylcholine in the prefrontal cortex and hippocampus by a mechanism that does not involve cholinergic autoreceptors (Shirazi-Southall et al., 2002; Tzavara, et al., 2006). It is unknown whether co-administration of an atypical antipsychotic drug and a cholinesterase inhibitor could raise the level of acetylcholine to a toxic threshold, or whether the anticholinergic properties of an atypical antipsychotic drug would cancel such a cholinergic overload or prevent beneficial effects of the cholinesterase inhibitor. A significant additional concern in the elderly is that a psychoactive drug, at its typical dose in young adults, might eventually lead to an adverse psychological side effect that is regarded not as a drug reaction but as an emerging new symptom of aging or a life event and therefore is treated with another psychoactive drug (which in turn may produce other psychological side effects).

After cerebral insults, the aged brain is fragile and especially sensitive to drug treatment. Retrospective clinical studies in stroke and trauma patients have demonstrated that some older drugs could retard func-

tional outcome, possibly through interfering with brain repair mechanisms (Goldstein, 1995, 1998). To facilitate neuroadaptations and to achieve lasting benefits in functional outcome, these detrimental drugs should perhaps be avoided. Our work in experimental stroke rats showed that, when used singly, several of the new CNS-active drugs used commonly among the elderly may be relatively safe with respect to possible cerebrovascular events or functional recovery, but only if they are discontinued (Zhao et al., 2005a–c).

Glutamate is the major excitatory neurotransmitter in the CNS acting through both ligand gated ion channels (ionotropic receptors) and G-protein coupled (metabotropic) receptors. NMDA receptor-mediated processes, in particular, play an important role in a variety of excitotoxic processes such as ischemia, oxidative stress, Alzheimer's disease (AD) and other age-related disorders (Karanian et al., 2006). NMDA receptor antagonists (e.g., memantine) designed to slow the progress of neural degeneration in early dementia patients may cause anterograde and retrograde amnesia and thus might interfere with cognitive function in the elderly (Creeley et al., 2006). In rats, memantine at threshold neuroprotective doses had no effect on acquisition of a hole-board task but was found to cause sensorimotor and movement side effects, and memory impairment 24 h after learning (Creeley et al., 2006). NMDA receptor antagonists and alcohol (which is an NMDA antagonist-like drug) can enhance functional outcome if delivered immediately after brain injury but can reinstate otherwise-recovered deficits if treatment is delayed (Kozlowski et al., 1994, 1997). Interestingly, the combination of caffeine and ethanol (caffeinol) delivered acutely after middle cerebral artery occlusion (MCAO) provides robust neuroprotection in animal models (Aronowski et al., 2003). Although it is unclear whether these common drugs would have a similar beneficial effect in elderly people sustaining a stroke, it has been shown that aged rats are much more vulnerable than young rats to alcohol-induced reaction time impairment despite comparable levels of brain alcohol (Spirduso et al., 1987).

3. Brain plasticity mechanisms in aging and stroke

Aging is a major risk factor for stroke, and aging populations pose a potentially huge burden to society as a whole. Despite this fact, the influence of aging on functional recovery following possible cerebrovascular injury is not well understood. Little is known about differences in neural adaptations in response to brain injury in the young vs. old brain, but older brains may be more vulnerable to minor focal infarcts and potentially to psychoactive drugs (Lindner et al., 2003). The capacity of neurons to create new synapses following partial denervation in the brains of aged rats is less robust than that of younger rats (Anderson et al., 1986). Older brains also may be less able to maintain compensatory adaptations for prolonged periods. In studies of rats that sustained

unilateral brain damage while young adults, recovery of motor function occurred but the symptoms re-emerged on the affected side during old age (Schallert, 1983, 1988). In another study, young and aged rats restored synaptic density to preoperative levels following a unilateral, intraventricular injection of kainic acid that destroyed the CA3–CA4 hippocampal pyramidal neurons. However, in the aged rats, this process required significantly more time, suggesting that the initial phase of synaptic replacement is retarded. Upregulation of growth-associated protein-43 (GAP-43) mRNA and neurite outgrowth in response to partial deafferentation also diminishes with age (Schauwecker et al., 1995). The upregulation of potentially restorative structural elements and increased levels of gene expression of neurofilament proteins are preserved after focal cerebral ischemia, but are diminished when compared to young animals (Popa-Wagner et al., 1999; Schroeder et al., 2003). One study suggests that a temporally anomalous gliotic reaction to cerebral ischemia in aged rats leads to the premature formation of scar tissue that impedes functional recovery after stroke (Badan et al., 2003). In addition, after cerebral ischemic stroke in aged rats, the upregulation and persistence of amyloidogenic proteins are exacerbated (Popa-Wagner et al., 1998). Furthermore, aged rats exhibit significant impairment of functional recovery, reduced vascular density, and reduced endothelial cell proliferation compared with young rats (Zhang et al., 2005b). A similar age-related decrease in plasticity may occur in humans (Mattay et al., 2002).

However, not all studies are consistent with the general view of increased vulnerability of motor functions with age. Jin et al. (2004) found that neural stem cells in the

subventricular zone (SVZ) of the aged brain (24-month) retained the capacity for proliferation and migration following cerebral ischemia, although the response is less robust than in younger animals (3-month). Recovery from impairment is surprisingly similar in young and aged rats following cortical photothrombosis, which suggests that the capacity to repair and maintain normal function can be retained in an aging brain (Fig. 1) (Zhao et al., 2005c). In one rat embolic model, more pronounced neurological impairment was observed in young animals (Shapira et al., 2002).

3.1. Altered excitatory and inhibitory neurotransmission

There is increasing evidence from animal studies indicating that an ischemic brain lesion leads to reduced activity of inhibitory neurotransmission by GABA receptors and overactivity of glutamate receptors resulting in hyperexcitability in widespread, structurally intact brain regions (Mittmann et al., 1998; Redecker et al., 2002). NMDA receptors are upregulated whereas GABA-A receptors are down-regulated in the ipsi- and contralateral neocortex after focal cerebral ischemia. Specific receptor subunits are downregulated at different locations within and surrounding a lesion site and in interconnected areas. Changes in subunit composition can influence receptor electrophysiology and are thought to contribute to hyperexcitability. Such changes could also thereby facilitate synaptic strengthening and seem to be tightly coupled with functional recovery. Also the contralateral hemisphere shows hyperexcitability, which is not restricted to brain areas homotopic to the lesion. Diazepam, a GABA

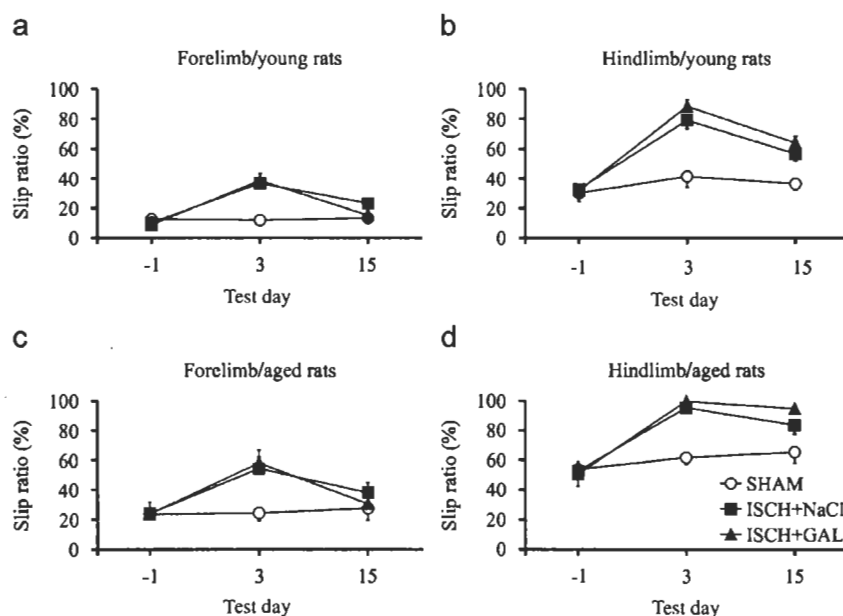


Fig. 1. Similar sensorimotor recovery for fore/hindlimb functions in young adult (5months) and aged (24 months) rats following cortical photothrombosis. Sensorimotor performance was assessed by the ledged beam-walking test. Steps onto the ledge were scored as a full slip and a half slip was counted if the limb touched the side of the beam. The slip ratio = (slips/total steps) \times 100% (These data are taken from Zhao et al., 2005c).

receptor agonist-like drug can interfere with recovery in rats following damage to the neocortex whereas pentylentetrazol, a GABA receptor antagonist, can accelerate recovery from sensorimotor cortex injury (Hernandez and Schallert, 1988; Schallert and Hernandez, 1998; Schallert et al., 1986). However, GABAergic agonists are not always detrimental to recovery (see Section 4.4.).

There is evidence from clinical studies that the hyperexcitable cortex may be a major substrate involved in stroke recovery. Reduced intracortical inhibition in the affected, but not the unaffected hemisphere, was found in one study with paired pulse transcranial magnetic stimulation (TMS) in stroke patients (Liepert et al., 2000); however, other studies have demonstrated reduced intracortical inhibition in the unaffected hemisphere in some patients (Butefisch et al., 2003; Cicinelli et al., 2003; Hummel and Cohen, 2006; Shimizu et al., 2002). Inconsistencies across studies are probably due to differences in the anatomical site of the lesions, chronicity of stroke, rehabilitation regimens, and degree of recovery (Harris and Eng, 2006; Huber et al., 2006; Kleim et al., 2003; Ward, 2004; Woodlee and Schallert, 2006). The influence of aging on injury related excitatory and inhibitory events, however, remains a major experimental gap.

3.2. Neuronal sprouting, reorganization and functional compensation

Local growth of axons and synapses could provide a mechanism following brain injury for intracortical remapping, which refers to changes in physiological or functional representations in the cortex. Consistent with this, molecular and cellular correlates of growth such as the GAP-43 protein and synaptophysin are increased in areas adjacent to infarct in rats (Rowntree and Kolb, 1997; Stroemer et al., 1998). Sprouting and arborization can also occur in remote brain areas of the undamaged hemisphere (Hsu and Jones, 2006; Jones and Schallert, 1994) and appear to be use- and injury-dependent. Sprouting and restoration of function in the aged rat may also be enhanced by anti-Nogo-A therapy (Markus et al., 2005).

During recent years, it has become clear that the adult brain maintains the ability to undergo extensive reorganization and functional re-deployment in response to impairments (Dancause et al., 2005; Dijkhuizen et al., 2003; Hanlon et al., 2005; Kleim et al., 2003; Rossini and Dal Forno, 2004; Ward, 2004). Reorganization can occur in regions adjacent to the lesion, in remote undamaged areas of the lesioned hemisphere, or in areas of the intact hemisphere. TMS motor mapping studies of the human motor cortex suggest that trophic factors such as brain derived neurotrophic factor (BDNF), which are altered by antidepressant drugs, may be involved in experience-dependent plasticity (Kleim et al., 2006). Following a focal lesion in the brain region controlling movements of one hand of squirrel monkeys, the cortical areas adjacent to the injury undergo use-dependent alterations in functional

topographic representations during the period of recovery (Nudo and Milliken, 1996; Nudo et al., 1996). This is a good example of local cortical reorganization occurring after central damage. Brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have also detected some evidence for local remapping in humans (Weiller et al., 1993). Plasticity can also occur in the remote undamaged areas of the lesioned hemisphere (Frost et al., 2003). There are clinical reports of patients who have suffered a second stroke (Fisher, 1992; Lee and van Donkelaar, 1995), from which it may be more difficult to recover.

A certain amount of recovery can be achieved through behavioral compensation rather than brain repair. Several studies have shown that compensatory movement strategies may come into play after brain injury in humans and animals (Friel and Nudo, 1998; Schallert, 1988; Schallert et al., 2002; Whishaw et al., 1991; Whishaw, 2000). It is often difficult, though not impossible, to disentangle true functional recovery from learned motor compensation (Schallert et al., 2002, 2003). Drugs that enhance motor learning, such as stimulants, may be useful in part because they enhance compensatory movements and strategies (Crisostomo et al., 1988; Feeney et al., 1982; Walker-Batson et al., 1995). Recovery of function attributable to motor learning may be less efficient in the elderly in relation to the extent that learning mechanisms are compromised by aging and by certain psychoactive drugs (e.g., those with NMDA, dopaminergic or cholinergic antagonist properties). Moreover, psychoactive drugs may affect brain temperature or food intake more extremely in the elderly, which could markedly influence neural events linked to neuroplasticity (Kleim et al., 2003).

3.3. Neurogenesis

Newborn neurons and other cells have been found in the adult SVZ and hippocampus. An important brain response to insults is neurogenesis and increased metabolic activity in the SVZ, hippocampus and possibly in the cortex (Jiang et al., 2001; Kolb et al., 2007; Lichtenwalner and Parent, 2006; Liu et al., 1998b; Valla et al., 1999). Basal neurogenesis in the subgranular and SVZ in aged rats is impaired, but both regions react in similar magnitude to stroke (Darsalia et al., 2005; Jin et al., 2004). In addition, striatal neuroblasts are generated without decline for at least 4 months after stroke in adult rats (Thored et al., 2006). Thus, neurogenesis is a potential repair mechanism in an injured brain, although its contribution to functional recovery remains unclear.

Interestingly, post-ischemic environmental enrichment increases neural stem/progenitor cell proliferation and migration toward the infarct (Komitova et al., 2005). Also, growth factors, statins and sildenafil increase neurogenesis in experimental stroke models (Zhang et al., 2005b). More importantly, electroconvulsive therapy (ECT) and chronic

antidepressant treatments such as tranylcypromine (mono-amino oxidase inhibitor) or fluoxetine (SSRI) increase adult hippocampal neurogenesis in rodents and primates (Malberg et al., 2000; Perera et al., 2007), and disrupting antidepressant-induced neurogenesis can block the behavioral responses to these drugs (Castren, 2004; Santarelli et al., 2003). Furthermore, antidepressant-induced neurogenesis is a region-specific effect. For example, the tricyclic antidepressant imipramine normalizes neurogenesis in the hippocampus and SVZ only, but not in the amygdala (Keilhoff et al., 2006). However, a recent study challenges the neurogenic effect of antidepressants by showing that these drugs increase both neurogenesis and neuronal elimination, which suggests that antidepressants increase the overall turnover of hippocampal neurons rather than simply cause neurogenesis (Sairanen et al., 2005). Antipsychotic drugs also can increase neurogenesis by blocking dopamine receptors (Halim et al., 2004; Kippin et al., 2005; Wang et al., 2004). It remains unclear whether drug induced increases in neurogenesis are functionally beneficial, or if they are harmful in some way.

4. CNS-active drugs and stroke recovery

The recovering brain remains sensitive to drug treatment and other manipulations such as rehabilitation (Biernaskie et al., 2004). Both experimental and human data suggest that certain classes of drugs affecting specific neurotransmitters can influence both the rate and ultimate degree of functional recovery after brain injury (Goldstein, 1995, 1998). Animal work suggests that there are sensitive periods during which the recovering brain is very vulnerable to the neural and behavioral effects of a drug. This vulnerability may also depend on the dose and duration of the drug treatment as well as the location and extent of the injury. For example, diazepam or other GABAergic agonist treatments within the first few days after a brain injury can be protective and beneficial, but continued use of the drug can exaggerate remote brain degeneration and disrupt functional recovery chronically even long after the drug is discontinued (Jones and Schallert, 1992; Schallert et al., 1986; Schallert and Lindner, 1990; Schallert and Hernandez, 1998). Delayed drug treatment can reinstate deficits that have diminished or disappeared in rats and people (Lazar et al., 2002, 2003; Schallert and Hernandez, 1998).

Elderly people, particularly those with brain injury, may have movement difficulties along with emotional and memory deficits. These problems may impose motor and cognitive impoverishment, which may in turn have an adverse effect on recovery and brain repair. In animals with brain injury, motor and cognitive enrichment can attenuate degeneration and improve functional outcome (Kleim et al., 2003). Importantly, social isolation may become a factor in the brain-damaged elderly, especially if they must live away from home and family. In rats, social isolation can increase infarct size (Craft et al., 2005). Sudden

isolation from cagemates immediately after injury can exaggerate secondary degeneration (Woodlee and Schallert, 2006). Social isolation also can reduce exercise induced neurogenesis (Stranahan et al., 2006). Psychoactive drugs may indirectly influence brain events linked to functional recovery through effects on social interactions, stress or other behavioral changes.

Drugs can affect functional recovery by enhancing or impairing brain plasticity processes. Drugs that promote the resolution of remote functional depression of brain regions connected to the primary site of brain damage (diaschisis) would be anticipated to be beneficial (Hernandez, 2006; Schmanke et al., 1996). However, the exclusive role of diaschisis in recovery is difficult to verify. Clinical observations suggest that improvement from crossed cerebellar diaschisis, at least, does not correlate with recovery after stroke (Bowler et al., 1995). Long-term potentiation (LTP) may be linked to learning and memory and contribute to functional recovery. Neurotransmitters such as dopamine (Otani et al., 2003), serotonin (Matsumoto et al., 2004; Ohashi et al., 2003) and GABA (Wigstrom and Gustafsson, 1985) can modulate LTP induction. In addition, dopamine, acetylcholine and nitric oxide systems have been shown to interact with each other to influence corticostriatal LTP-like events or long term depression (LTD) triggered in response to repetitive synaptic stimulation (Centonze et al., 2003). Moreover, structural reorganization plays an important role in drug action (Stroemer et al., 1998). On the other hand, some psychotropic drugs such as new antidepressants may induce neurogenesis and promote brain repair (Castren, 2004; Malberg and Schechter, 2005; Santarelli et al., 2003), although it is not clear whether mitotic activity functionally replaces lost cells.

Retrospective clinical studies have shown that the detrimental drugs examined in rodents often have a similar impact in humans recovering from stroke (Goldstein, 1995, 1998). This notion is also supported by a recent study in six inpatient rehabilitation hospitals in the USA, which showed that first-generation selective serotonin uptake inhibitors, older traditional antipsychotics and anti-parkinsonian drugs have a statistical association with poorer outcome (Conroy et al., 2005). Interestingly, a significant variation in choice of medication was observed, which could not be explained by patient differences. Physician preferences seemed to be primary determinants of medication choice. Analysis of the same post-stroke rehabilitation outcomes project (PSROP) database showed that the use of neurostimulant medication (e.g., methylphenidate, modafinil, levodopa, amantadine, bromocriptine) did not affect length of stay, motor recovery, cognitive recovery, or discharge destination (Zorowitz et al., 2005). We will next review experimental and patient studies, primarily from 1995 onward, that describe the effects of individual therapeutic classes of CNS-active medication on stroke recovery. Table 1 lists the most recent (2000–2006) studies of CNS-active drug effects in focal ischemia models that

Table 1
Recent studies of CNS-active medication on behavioral and histological outcome in experimental stroke and brain injury models (2000–2006)

Drug	Model	Dose	Outcome measure	Comments	Ref.
<i>Cholinergic drugs</i>					
Galantamine	Rose Bengal	2.5 mg/kg, daily	Beam, water-maze	No effects	(Zhao et al., 2005c)
<i>Antidepressant</i>					
Fluoxetine	Transient MCAO	5 mg/kg, 10 days	Limb-placing, water-maze	No significant effects	(Jolkkonen et al., 2000)
Fluoxetine	Endothelin-1	10 mg/kg, 4 weeks	Cylinder, staircase	No significant effects	(Windle and Corbett, 2005)
Fluoxetine	Rose Bengal	5 mg/kg, daily	Beam, water-maze	No significant effects	(Zhao et al., 2005a)
<i>Antiparkinsonian</i>					
Selegiline	Transient MCAO	0.5 mg/kg, daily	Limb placing, staircase, water-maze	Improved water-maze when with enriched environment	(Puurunen et al., 2001)
<i>Antipsychotics</i>					
Clozapine, haloperidol	Cortical ablation	Clozapine 0.1–1.0 mg/kg Haloperidol 0.1–10 mg/kg	Beam-walking	Significant impairment after haloperidol	(Goldstein and Bullman, 2002)
Risperidone	Rose Bengal	1 mg/kg, daily	Beam, water-maze	Acute impairment	(Zhao et al., 2005a)
<i>GABAergic</i>					
Lamotrigine	Transient MCAO	5–20 mg/kg, iv, acute	Strength and agility	No effects	(Traystman et al., 2001)
Zopiclone	Rose Bengal	3 mg/kg, daily	Beam, water-maze	Sensorimotor improvement	(Zhao et al., 2005b)
<i>Others</i>					
Lithium	Transient MCAO	0.5–3 mEq/kg for 1 week	Neuroscore	Improved motor function, cell protection	(Ren et al., 2003)

include behavioral outcome measures. Earlier studies having behavioral and/or histological measures are included in the text of this review. Table 2 lists recent clinical studies (1996–2006) of CNS-active drug effects on stroke outcome. An extensive list of unpublished and/or ongoing studies related to this topic can be found at <http://strokecenter.org/trials> and <http://clinicaltrials.gov>.

4.1. Antidepressants

Antidepressants alter synaptic concentrations of monoamines, which reasonably might promote recovery of function. More importantly, recent data indicate that antidepressants are involved in the signal pathway of neurotrophins and cAMP response element-binding protein (CREB). Furthermore, chronic antidepressant treatments increase adult hippocampal neurogenesis as discussed in Section 3.3.

Traditional antidepressants such as amitriptyline and desipramine, and selective serotonin reuptake blockers, including trazodone and fluoxetine, have been claimed to have a differential effect on recovery (Boyeson and Harmon, 1993; Boyeson et al., 1994). Following unilateral sensorimotor cortex lesions in rats, a single dose of desipramine facilitates motor recovery. In contrast, a single injection of trazodone 24 h after injury transiently impaired

motor recovery. A reinjection of trazodone reinstated the hemiparesis for up to 6 h in recovered rats (Boyeson and Harmon, 1993). Amitriptyline, a mixed serotonin and noradrenergic reuptake blocker with α_1 -adrenergic receptor blocking activity, has no demonstrable effect on motor recovery after experimental focal brain injury (Boyeson et al., 1994). Recent data with fluoxetine are variable with minor beneficial or no significant effect on the recovery process in both young and old stroke animals (Jolkkonen et al., 2000; Windle and Corbett, 2005; Zhao et al., 2005a).

Antidepressants are widely used for the treatment of post-stroke depression, an important complication of stroke (Kauhanen et al., 1999; Kotila et al., 1999). However, stroke patients' safety, particularly their cardiovascular health, has become a major concern (Barbui et al., 2005; Ramasubbu, 2004; Rampello et al., 2005). Interestingly, in a small number of stroke patients, fluoxetine, when coupled with physical therapy, was shown to improve functional recovery (Dam et al., 1996). Discrepancies between patient and experimental studies might be explained by the alleviation of depression. Depression is a predictor of worsened outcome, and it may be that by improving depressive symptoms (Cole et al., 2001; Kimura et al., 2000; Kotila et al., 1999), patients achieve a higher level of recovery simply because they are more motivated to engage in rehabilitation.

Table 2
Recent studies of CNS-active medication on functional outcome in stroke patients (1996–2006)

Drug	Dose	Outcome measure	Comments	Ref.
<i>Cholinergic drugs</i>				
Donepezil	5 mg daily for 4 weeks + 10 mg for 12 weeks	Fugl-Meyer, Rivermead mobility	Improved sensorimotor function in the lower limb and shoulder	(Berthier et al., 2003)
Donepezil	5 mg for 2 weeks and CIT	Wolf motor function test, Fugl-Meyer, Caregivers Strain index	Nonsignificant improvement in WMFT	(Nadeau et al., 2004)
Donepezil	5 or 10 mg for 28 days	Alzheimer's Disease Assessment Scale, CIBIC-plus	Significant improvement in cognition	(Wilkinson et al., 2003)
<i>Antidepressant</i>				
Fluoxetine	20 mg daily for 3 months	HSS and Barthel Index	Significant benefit when combined with physiotherapy	(Dam et al., 1996)
Fluoxetine	A single dose, 20 mg	fMRI, the nine peg hole test, dynamometer, finger tapping	Improvement in motor skills, hyperactivation of motor cortex	(Pariente et al., 2001)
Maprotiline	150 mg daily for 3 months	HSS and Barthel Index	Detrimental	(Dam et al., 1996)
Moclobemide	600 mg daily for 6 months	Reinvang's 'Grunntest, Amsterdam-Nijmegen-Everyday-Language-Test	No significant benefit	(Laska et al., 2005)
<i>Antiparkinsonian</i>				
L-DOPA	100 mg for 3 weeks with physiotherapy	Rivermead motor assessment	Significant improvement in motor recovery	(Scheidtmann et al., 2001)
Selegiline	5 mg twice a day for 3 months	SSS, BI, FM, ZDS,15-D	Significant benefit	(Sivenius et al., 2001)
<i>GABAergic</i>				
Midazolam	0.5 mg intravenous	Boston Naming Test and the Dictated Medical Research Council rating scale	Detrimental	(Lazar et al., 2003)
<i>Others</i>				
Methyphenidate	5–30 mg for 3 weeks	Fugl-Meyer Scale, Functional Independence Measure	Improvement in motor functions, lower score for depression	(Grade et al., 1998)

The work by Paolucci et al. (2001) confirmed the unfavorable influence of depression on functional outcome, despite improved depressive symptoms due to antidepressant use (mainly fluoxetine). In addition, cortical plasticity may be involved, as suggested by fMRI examination, which showed hyperactivation in the ipsilesional primary cortex and associated improvement of motor performance after a single dose of fluoxetine in stroke patients (Pariente et al., 2001).

4.2. Antipsychotics

The typical antipsychotic, haloperidol, which is a dopamine receptor antagonist and potential noradrenergic receptor blocker, may be harmful to motor recovery in rats and perhaps also in stroke patients (Feeney et al., 1982; Goldstein, 1995). The detrimental effects of haloperidol may be partially due to dopamine receptor blockage in the striatum (Crocker and Hemsley, 2001). In addition, rats treated with 0.30 mg/kg haloperidol were impaired in the

Morris water maze, compared to rats treated with vehicle following traumatic brain injury; whereas the third-generation neuroleptic, olanzapine, did not impair cognitive performance (Wilson et al., 2003). There is also evidence showing that both typical and atypical neuroleptics can regulate brain plasticity via the genes involved in synaptic structure and function. It seems that the interaction between dopamine and glutamate is one of the important mechanisms in this process, since co-activation of dopamine D₁ and glutamate NMDA receptors is required for eliciting the long-term changes associated with plasticity (Gemperle et al., 2003; Meltzer, 2004).

The absence of any detectably harmful effect of risperidone on recovery following stroke was also found in our animal study (Fig. 2) (Zhao et al., 2005a). In this study, aged Wistar rats (24 months) were treated with risperidone at a dose of 1 mg/kg (i.p., once a day) starting 7 days before focal cortical photothrombosis and continuing for 28 days thereafter. Sensorimotor recovery was assessed by the ledged beam-walking test and spatial

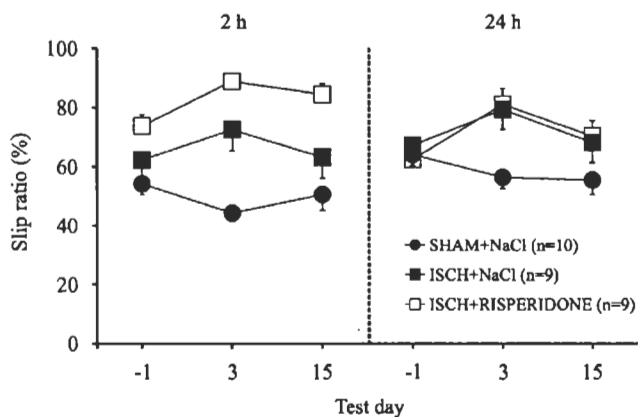


Fig. 2. Impaired performance for hindlimb as measured by the ledged beam-walking test in aged rats subjected to cortical photothrombosis and treated with risperidone. Sensorimotor function is impaired only when tested acutely (2 h) after drug administration. The slip ratio = (slips/total steps) \times 100% (These data are taken from Zhao et al., 2005a).

learning by the Morris water-maze before cortical stroke, immediately after stroke, and at the end of follow-up. Infarct volumes were measured from nitroblue tetrazolium-stained sections at the end of follow-up. The high slip ratio for the contralateral hindlimb in ischemic rats treated with risperidone indicated sensorimotor impairment when tested 2 h after drug administration. Sensorimotor impairment was not observed, however, when the rats were tested 24 h after risperidone administration. Similarly, water-maze performance was impaired 2 h after risperidone. Cortical infarct volumes were not different in ischemic controls and ischemic rats treated with risperidone. Also the work by Goldstein and Bullman showed that the atypical antipsychotic clozapine did not affect motor recovery after cortical ablation, whereas haloperidol impaired performance (Goldstein and Bullman, 2002).

The use of new atypical neuroleptics, such as clozapine, risperidone or olanzapine which can block dopamine and serotonin receptors has raised concern about possible cerebrovascular events (Gareri et al., 2006; Percudani et al., 2005; Wooltorton, 2002, 2004). A more recent large retrospective, population-based cohort study identified 11,400 elderly patients who had been given treatment with a neuroleptic from 1997 to 2002 (Herrmann et al., 2004). Olanzapine and risperidone did not lead to a significant increase in stroke risk compared to typical neuroleptics. Also, Gill et al. found a similar risk of ischemic stroke between patients taking typical and atypical antipsychotics (Gill et al., 2005). The effect of atypical antipsychotics on functional outcome in stroke patients remains open.

4.3. Cholinergic drugs

The cholinergic system is involved in brain excitability and plays an important role in attention, cognition and arousal (Everitt and Robbins, 1997; Sarter, 2006; Wenk,

1997). Lesions to the basal forebrain cholinergic system impair cortical reorganization and motor learning, which supports the idea that the cholinergic system is involved in neural plasticity associated with learning (Conner et al., 2003). Furthermore, a recent study has indicated that adult neurogenesis is at least partly regulated by the cholinergic system. A selective lesion of the basal forebrain decreases the number of cholinergic cells colocalized with bromodeoxyuridine (BrdU) and the neuronal nuclei marker NeuN in the granule cell layers of the dentate gyrus and olfactory bulb (Cooper-Kuhn et al., 2004). Consistent with this, donepezil treatment increased BrdU-positive cells in the hippocampus (Kotani et al., 2006). More interestingly, in adult rats, the basal forebrain cholinergic system induces whisker functional representation through nerve growth factor (Prakash et al., 2004). There is scattered evidence that the administration of cholinergic agonists may enhance recovery of function (Feeney and Sutton, 1987) and anticholinergic drugs, such as scopolamine, may interfere with recovery (De Ryck et al., 1990). However, in aged rats we found that the cholinesterase inhibitor galantamine was neither beneficial nor detrimental with respect to histological or functional outcome after experimental stroke (Zhao et al., 2005c).

The available patient studies suggest that acetylcholinesterase inhibitors might affect sensorimotor functions after stroke. A case report showed that donepezil improved sensorimotor function in the hemiplegic lower limb and shoulder (Berthier et al., 2003). This was also reflected in an enhancement of ipsilateral motor representations during active movements of the left shoulder. Another study combined donepezil treatment with constraint-induced therapy (CIT) (Nadeau et al., 2004). CIT had substantial and significant effects on outcome as measured by the Wolf Motor Function test and the Motor Activity Log. However, donepezil as an adjuvant to CIT had only a nonsignificant effect on these outcome measures. People who have been taking cholinesterase inhibitors chronically may have downregulated cholinergic receptors, as is found in animals (Schallert et al., 1980). It is possible that if the drugs are discontinued, particularly after a stroke, the reduced density of cholinergic receptors could have adverse effects.

The efficacy of acetylcholinesterase inhibitors has also been evaluated in patients with vascular dementia. For example, patients who received donepezil, 5 or 10 mg every day for 28 days showed significant improvement in their cognitive function compared to those taking placebo, as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) (Wilkinson et al., 2003). Evaluation of global function also revealed significant improvements for patients at both doses of donepezil, compared to patients who received placebo, as measured by the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC-plus). Similarly, rivastigmine and galantamine improve cognition in vascular dementia patients (<http://strokecenter.org/trials/>).

4.4. GABAergic drugs

Drugs acting on the GABAergic system may also affect the recovery process. Benzodiazepines, such as diazepam and barbiturates can disrupt or interfere with recovery, depending on the site of injury (Hernandez and Holling, 1994; Schallert et al., 1986). For example, long-term administration of diazepam permanently impedes recovery from the sensory asymmetry caused by anteromedial neocortex damage in the rat (Schallert et al., 1986), but not sensorimotor cortex (Jones and Schallert, 1992). The effects of the GABAergic system on recovery after brain damage are likely to be due to the major inhibitory action of GABA (Macdonald and Olsen, 1994) and the resulting modification of brain plasticity (Skangiel-Kramska et al., 1994; Ziemann et al., 1998). In addition, GABAergic intracortical connections may play an important role in mediating cortical reorganization (Jacobs and Donoghue, 1991). GABA receptor agonists delivered acutely can be neuroprotective and may rescue neurons in the substantia nigra pars reticulata, ventrolateral and ventromedial nuclei of the thalamus, and hippocampus after brain injury (Schallert and Hernandez, 1998). Thus, the total effect of GABAergic drugs on recovery following brain injury depends on the time of administration.

We examined the GABAergic agonist zopiclone in aged rats with a focal infarct to the sensorimotor cortex. (Zhao et al., 2005b). In this study, aged Wistar rats (24-months) were treated with zopiclone at a dose of 3 mg/kg (i.p., once a day) beginning 4 days before ischemia induction and continuing for 23 days. Sensorimotor recovery was assessed by a ledged beam-walking test designed to detect behavioral compensation vs. brain repair, and spatial learning by the Morris water-maze. After a 7-day washout period all rats were administered a single dose of zopiclone (3 mg/kg, i.p.) and retested. Beam-walking data showed that ischemic rats treated with zopiclone were not more impaired than untreated rats. Indeed, they showed fewer faults with the impaired hindlimb than ischemic controls on post-operative day 16. The site of the infarct was likely a factor in these results (Jones and Schallert, 1992). Water-maze performance was not affected by zopiclone. After the washout period a single dose of zopiclone did not worsen forelimb or hindlimb function, and improved performance in the water-maze test. It is possible that zopiclone reduced fearfulness or anxiety in aged rats, which may be sensitive to stressful test conditions. For example, amitriptyline is believed to improve water-maze performance through this mechanism (Yau et al., 2002). Importantly, zopiclone did not affect infarct volume.

Clinical studies on new GABAergic drugs in stroke patients are scarce. This is alarming given the high number of patients treated with sedatives or gabapentin for pain relief (Conroy et al., 2005). As noted previously, midazolam may re-induce neurological deficit in transient ischemic attack (TIA) and stroke patients (Lazar et al., 2002, 2003), consistent with the effects of diazepam or

alcohol in rats (Kozlowski et al., 1997; Schallert and Hernandez, 1998) indicating the possible involvement of a GABA-A-mediated mechanism in maintaining post-stroke recovery. The early GABAergic activation study in stroke (EGASIS) study showed that diazepam given within 12 h may not be beneficial when independence is the primary outcome measure (Lodder et al., 2006). This does not support the general notion of the neuroprotective role of GABAergic drugs during the acute phase. This is also consistent with the experimental study showing no neuroprotection by diazepam in rats with MCAO when normothermia is maintained (Kuhmonen et al., 2002).

4.5. Parkinson's disease medication

Levodopa and direct dopamine receptor agonists are effective symptomatic treatments for Parkinson's disease, and all patients receive at least one of these agents during their illness. One must note that anti-Parkinson's medication has entirely different implications in the absence of Parkinson's disease. For example, in the study of Conroy et al. (2005) only 3.9% of the patients using anti-Parkinsonian medication had a documented Parkinson's disease.

The work by Scheidtmann et al. supports the role of dopamine in stroke recovery (Scheidtmann et al., 2001). Patients in the study received 100 mg of levodopa for 3 weeks in combination with physiotherapy. Motor recovery was significantly improved in levodopa treated patients and this was maintained after treatment was stopped. The mechanism(s) underlying the beneficial effect of levodopa remain open, but noradrenaline could be involved. Interestingly, a single dose of levodopa enhances the ability of motor training to encode an elementary motor memory relative to placebo (Floel et al., 2005). Selegiline (l-deprenyl) is a selective irreversible monoamine oxidase B (MAO-B) inhibitor that is used in the treatment of Parkinson's disease. Selegiline also has neuroprotective and neuronal rescuing properties independent from its MAO-B activity. In MCAO rats, selegiline improves cognitive outcome especially when combined with housing in an enriched environment (Puurunen et al., 2001). Also, a phase II study in 24 stroke patients showed that 5 mgs of selegiline given twice a day for 3 months improves motor functions as measured by the Scandinavian Stroke Scale (Sivenius et al., 2001). Bromocriptine, a dopamine D2 receptor agonist, did not improve aphasia after stroke (Ashtary et al., 2006).

4.6. Others

Other drugs specifically used for their effects on the central nervous system have been less studied. Use of neurostimulant medication may be relevant with respect to stroke rehabilitation. Although data from the PSROP database suggested that neurostimulant medication has no effect on motor recovery (Zorowitz et al., 2005), a study

with 21 stroke patients showed that 5–30 mg of methylphenidate given daily for 3 weeks improved motor functions as measured by the Fugl–Meyer Scale and Functional Independence Measure (Grade et al., 1998).

One has to note that the recent evidence on brain plasticity has prompted increasing interest in possible recovery enhancing drugs. These compounds are not discussed here. Regarding amphetamine, readers are referred to recent reviews (Martinsson and Eksborg, 2004; Martinsson et al., 2003).

5. Conclusions

The central nervous system can adapt to injury and degeneration throughout the lifespan (Bavelier and Neville, 2002; Chen et al., 2002). After cerebral insults, however, the aged brain may be somewhat more fragile than the young adult. Retrospective clinical studies in stroke and trauma patients have demonstrated that some older drugs retard functional outcome, possibly through brain repair mechanisms (Goldstein, 1995, 1998). However, single use of new psychotropic drugs seems to be relatively safe with respect to possible cerebrovascular events or functional recovery in the elderly. More alarming is inappropriate polypharmacy, which may result in unexpected drug interactions and side effects in the central nervous system. Based on known properties of psychoactive drugs used in the elderly, one or more mechanisms of action of a drug might be counteracted or exaggerated by the mechanism(s) of action of another drug. Very little is known about the effects of continuing vs. discontinuing drugs after stroke, or the optimal times for drug administration, particularly when several drugs are used. The risks and benefits of CNS active medication have to be carefully considered in order to decrease possible complications and increase the quality of life of stroke survivors.

Different degrees of functional recovery, weeks or months after the ischemic event, are observed in clinical practice (Kwakkel et al., 2004) and have been related to restitution of the ischemic penumbra, resolution of diaschisis, and endogenous self-repair mechanisms (Kwakkel et al., 2003). The growing understanding of the mechanisms involved in the phenomena of brain plasticity and their modulation may open up new directions in the treatment of stroke patients. This may take place by, first, restoring functional deficits, and then encouraging endogenous neurogenesis with intensive task-oriented rehabilitation supported by appropriate use of CNS-active medication.

Animal research remains critical to the understanding of basic mechanisms of injury and recovery because it can be conducted without the ethical restriction of randomization of treatment or confounding factors such as age, sex, other diseases, compliance, and appropriateness of use (Turkstra et al., 2003). Thus, controlled experimental approaches might help to address the safety of psychotropic drugs and

should be used to support epidemiological and clinical studies.

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