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Psychotropic Medication and Functional Recovery following Cortical Stroke in Aged Rats

Doctoral dissertation

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ABSTRACT

Recovery process following cerebral insults such as stroke is affected by aging and can be modulated by pharmacotherapy. The purpose of this series of studies was to evaluate the effect of new psychotropic medications on the histological and functional outcome following cortical stroke in aged rats which might be more vulnerable to brain insults. This follows clinical practice in which elderly patients who are taking psychotropic medication sustain small focal strokes. We evaluated the effects of galanthamine, a selective competitive cholinesterase inhibitor, risperidone, an atypical neuroleptic, alone or in combination with fluoxetine, a selective serotonin reuptake inhibitor, and zopiclone, a hypnotic drug. Acute and chronic drug effects or the effects after a washout period on sensorimotor performance and spatial learning were studied by a novel tapered beam-walking task and match-to-place version of the Morris water-maze test, respectively. The main results were: 1) galanthamine is not beneficial or harmful with respect to the histological or functional outcome in young or aged rats subjected to cortical photothrombosis, 2) risperidone does not affect histological or long-term functional outcome in aged rats subjected to cortical photothrombosis, but its extrapyramidal side effects are likely to acutely impair behavioral performance, 3) fluoxetine alone or in combination with risperidone did not affect histological or behavioral outcome, and 4) long-term administration of zopiclone, did not worsen functional outcome, and even slightly improved behavioral performance following cortical infarct in aged rats. Taken together, the present data demonstrate that aged rats can undergo a remarkable functional recovery after being subjected to cortical stroke. New psychotropic drugs used commonly in the elderly seem to be relatively safe with respect to sensorimotor and cognitive recovery once the treatment was discontinued. Infarct volumes were not affected by the studied drugs.

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To my wife, Mei Zhao

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Chuan-sheng Zhao

ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxasole propionic acid
ANOVA	analysis of variance
CA1-4	subfields of hippocampus
cAMP	adenosine 3',5'-cyclic monophosphate
CNS	central nervous system
CREB	cyclic AMP responsive element binding protein
DNA	deoxyribonucleic acid
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GAP-43	growth associated protein-43
i.p.	intraperitoneal
LTP	long-term potentiation
mRNA	messenger ribonucleic acid
NBT	nitroblue tetrazolium
NMDA	N-methyl-D-aspartate

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following publications that are referred to in the text by the Roman numerals I-IV.

I **Chuan-sheng Zhao,** Kirsi Puurunen, Timothy Schallert, Juhani Sivenius, Jukka Jolkkonen. Psychotropic medication and stroke outcome. **American Journal of Psychiatry** 2005;162:1026-1027.

II **Chuan-sheng Zhao,** Kirsi Puurunen, Timothy Schallert, Juhani Sivenius, Jukka Jolkkonen. Effect of cholinergic medication, before and after focal photothrombotic ischemic cortical injury, on histological and functional outcome in aged and young adult rats. **Behavioural Brain Research** 2005;156:85-94.

III **Chuan-sheng Zhao,** Kirsi Puurunen, Timothy Schallert, Juhani Sivenius, Jukka Jolkkonen. Behavioral and histological effects of chronic antipsychotic and antidepressant drug treatment in aged rats with focal ischemic brain injury. **Behavioural Brain Research** 2005;158:211-220.

IV **Chuan-sheng Zhao,** Kirsi Puurunen, Timothy Schallert, Juhani Sivenius, Jukka Jolkkonen. Behavioral effects of photothrombotic ischemic cortical injury in aged rats treated with the sedative-hypnotic GABAergic drug zopiclone. **Behavioural Brain Research** 2005;160:260-266.

CONTENTS

1. INTRODUCTION

Although a decrease in risk factors as well as 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, is surpassed only by heart disease and cancer and is a leading cause of disability in adults (Ingall 2004, Kelly-Hayes 2004). Despite extensive research, acute stroke treatments are limited to thrombolysis within 3 hours of symptom onset (Markus 2005). Thus, effective and safe treatments to prevent or restrict the acute neuronal damage occuring after stroke are needed.

Most stroke patients show some degree of spontaneous functional recovery from their initial disabling state (Nakayama et al. 1994, Arboix et al. 2003). The extent of recovery depends primarily on the size and location of the cerebral infarction. Early recovery following stroke is thought to be due to the resolution of cerebral edema, absorption of damaged tissue or reperfusion of the ischemic penumbra. At later stages of recovery, neurite growth and synaptogenesis take place, leading to the functional and structural reorganization of the remaining intact brain tissue. Brain imaging studies have proved that intact brain can compensate for functions lost after brain damage (Dijkhuizen et al. 2001, Bütefisch et al. 2003, Dijkhuizen et al. 2003, Rossini and Dal Forno 2004, Ward 2004, Hanlon et al. 2005). Overgrowth of dendrites and synapse formation may occur in both hemispheres following unilateral damage to the forelimb representation area and this process occurs in parallel with the time of functional recovery (Jones and Schallert 1994).

Both experimental and human studies suggest that the age of the individual has an important impact on the functional recovery after brain damage (Carr et al. 1993, Popa-Wagner et al. 1999). Brain physiology and neurochemistry change during aging and alter the neurobiological response to brain insults. Although stroke is strongly associated with advanced age, most data are based on experiments conducted on young animals. This is despite the recommendation by the STAIR committee (STAIR 1999) and the more recent

Stroke Progress Review Group suggesting that the data from aged animals might be considered as more appropriate from a preclinical standpoint than that obtained from young adults. Pharmacotherapy has also an effect on functional recovery after stroke. 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, Feeney and Westerberg 1990, Feeney et al. 2004). Clinical studies have shown that the same drugs (*e.g.,* amphetamine, clonidine, prazosin, dopamine receptor antagonists, benzodiazepines, phenytoin) have a similar impact in humans recovering from stroke (Crisostomo et al. 1988, Goldstein 1995, Walker-Batson et al. 1995).

It is very common that stroke patients are prescribed with neuroleptics, antidepressants, cholinesterase inhibitors, and sedatives pills for the treatment of complications and coincident disorders (Goldstein 1995, Perry et al. 2000, Lampl et al. 2002, Berthier et al. 2003, Black et al. 2003, Donnan et al. 2003, Leker and Neufeld 2003, Eriksson et al. 2004, Erkinjuntti et al. 2004, Fogelholm et al. 2004, Kappelle and Van Der Worp 2004). More importantly, increasing amount of new psychotropic medicines are being prescribed without a understanding of their effects on possible cerebrovascular events or functional recovery after a stroke. On the other hand, some psychotrophic drugs such as new antidepressants may induce neurogenesis and promote brain repair (Santarelli et al. 2003, Castren 2004).

The purpose of this thesis was to evaluate the effects of psychotropic medication on histological and functional outcome in aged rats following cortical stroke. The aim was to model clinical practice in which elderly patients who are taking psychotropic medication sustain small focal strokes. The Rose Bengal model was selected to produce a cortical infarct, because the brain pathology is well characterized, the cortical lesion produced is consistent, craniectomy is not needed, and the lesion has a precise location and size. Aged rats were used since they might be more vulnerable to brain insults. Challenging and sensitive behavioral tests were used to assess functional outcome.

2. REVIEW OF LITERATURE

2.1. NEUROCHEMICAL, STRUCTURAL AND FUNCTIONAL CHANGES DURING AGING

2.1.1. Shrinkage and neuronal loss in the aged brain

The most striking feature of aging brain is shrinkage. This takes place in several brain areas including the frontal cortex, the striatum and midbrain structures such as the locus coeruleus and substantia nigra (Raz 2001, Raz et al. 2004, Raz et al. 2005). Age-related shrinkage also coincides with the expansion of the ventricular volume (Raz et al. 1995, Matsumae et al. 1996, Raz et al. 1997, Gunning-Dixon et al. 1998, Raz et al. 1999). The general view of aging causing a global decrease in the number of neurons (Brody 1955, Henderson et al. 1980, Coleman and Flood 1987) is changing to one of relative neuronal preservation (Merrill et al. 2000, Merrill et al. 2001, Rapp et al. 2002, Rutten et al. 2003), although individual variability is marked.

Significant age-related loss of dendritic morphology is likely to contribute to shrinkage (Jacobs et al. 1997, de Brabander et al. 1998, Grill and Riddle 2002). The age-related regressive dendritic loss includes both dendrites shortening and fewer dendritic branches (Anderson and Rutledge 1996, Jacobs et al. 1997). Loss of dendritic spines is another consistent change encountered during aging (Jacobs et al. 1997, Itzev et al. 2003).

Both experimental and human studies reveal a significant loss of synapses with age (Masliah et al. 1993, Geinisman 1999, Peters 2002, Shimada et al. 2003). This structural change also displays regional specificity. In addition to synaptic loss, there is age-related modification of synaptic structure, *e.g.*, fewer synaptic vesicles within neurons and a smaller presynaptic area (Adams and Jones 1982). There is evidence that some neurons dramatically lose synaptic input, *e.g.*, aged mice exhibit both smaller excitatory postsynaptic potential amplitudes and

fewer synaptic boutons. The number of synaptic contacts is also significantly lower in aged animals (Coggan et al. 2004). However, there is also contrasting evidence regarding age-related changes in synaptic morphology (Brown et al. 1998, Scheff et al. 2001).

2.1.2. Changes in neurochemistry and neurotransmission during aging

Age-related molecular changes include elevated levels of oxidative stress and associated oxidative damage to proteins and DNA (Edwards et al. 1998, Dorszewska and Adamczewska-Goncerzewicz 2004, Poon et al. 2004), multiple altered signal transduction pathways (Fulop and Seres 1994, Zhen et al. 1999, Pasquare et al. 2004), impaired cellular metabolism (Mattson et al. 1999), and mitochondrial dysfunction (Xiong et al. 2002, Ames 2004, Bertoni-Freddari et al. 2004), which is associated with an increase in damage to mitochondrial DNA as a result of oxidative damage and lack of effective DNA repair (Schapira 1996, Sastre et al. 2000). There are many other crucial neuronal changes found during ages, *e.g.*, dysregulation of proteins involved in neuronal structure and signaling and upregulation of many proteases that play essential role in regulating neuropeptide metabolism, amyloid precursor protein processing, and neuronal apoptosis (Jiang et al. 2001).

Neurochemical changes in the brain during aging have been extensively documented (Uchida et al. 1995, Wardas et al. 1997, Miguez et al. 1999, Lee et al. 2001, Segovia et al. 2001, Miura et al. 2002). It seems that the different neurotransmitter systems are affected differentially by aging and this also varies by brain regions. For example, monoaminergic neurotransmission declines during aging. A marked decrease in dopamine, serotonin and 5-hydroxyindolacetic acid, the major metabolite of serotonin, are observed in the cerebral cortex in aged rats (Lee et al. 2001). A decrease in the concentration of acetylcholine with aging has also been demonstrated (Ogawa et al. 1994, Stemmelin et al. 2000). In addition, data from human and animals reveal prominent age-related decreases in the densities of dopamine receptor subtypes in cortex and hippocampus (Kaasinen et al. 2000, Inoue et al.

2001, Hemby et al. 2003). Density of noradrenergic receptors has also been reported to decline with age in the frontal, temporal cortex and hippocampus (Kemper 1994). However, also contradictory results exist on age-related changes in different neurotransmitter systems (Harik and McCracken 1986, Moretti et al. 1987, Robson et al. 1993, Magnone et al. 2000).

Concentrations of asparagine, glycine, taurine, and alanine increase significantly with age, while glutamine, arginine, and threonine concentrations do not change (Hare et al. 1982, Tohgi et al. 1993). Wheeler and Ondo (1986) compared the γ-aminobutyric acid (GABA) concentration in cortical synaptosomes from young male rats and aged rats and found a decrease in the GABA content with age. Activity of the GABA transporter in the hypothalamus and cortex also decreases significantly with age (Wheeler 1982, Wheeler 1983). Binding to $GABA_A$ receptors in aged brains is either lower than (Govoni et al. 1980, Nabeshima et al. 1994), or similar to the level of that in young rats (Wenk et al. 1991, Ruano et al. 1996) or modified in terms of subunit composition (Caspary et al. 1999). Interestingly, a consistent decrease in $GABA_B$ receptor binding has been observed in the aged brain (Milbrandt et al. 1994, Turgeon and Albin 1994, Ichida and Kuriyama 1998).

Perhaps the most consistent age-related change is the loss of glutamate receptors in a number of brain regions including the hippocampus (Carpenter et al. 1992, Cohen and Muller 1992, Villares and Stavale 2001). In addition to a decrease in N-methyl-D-aspartate (NMDA) receptors, different NMDA receptor subunits display age-related modifications (Laurie et al. 1997). It has been noted that aged rats show an expression deficit in the C2 splice variant of the NR1 subunit (Clayton et al. 2002). In Fischer 344 rats, an age-related decrease in the NR1 and NR2B NMDA receptor subunits has also been observed (Mesches et al. 2004). In the cerebral cortex of 30-month-old mice, protein expression of both the NR2B and NR1 subunits of the NMDA receptor were decreased significantly compared to the levels found in 3- and 10-month-old mice (Magnusson et al. 2002). Protein expression of the NR2A subunit also revealed a significant age-related decline. In the hippocampus, the NR2B subunit exhibited a higher expression level in 10-month-old mice as compared to both young and old

mice. There was a significant decline in the expression of the NR1 subunit in old mice. Binding studies revealed a significant decrease in NMDA but preserved α-amino-3-hydroxy-5-methyl-4-isoxasole propionic acid (AMPA) and kainate receptors with age (Tamaru et al. 1991, Nicolle and Baxter 2003).

2.1.3. Functional changes

A decline in learning and memory with age is well-documented both in experimental and human studies (Luszcz and Bryan 1999, Small 2001, Albert 2002, Stoelzel et al. 2002, Gallagher et al. 2003, Stemmelin et al. 2003, Wilson et al. 2003, Brightwell et al. 2004, Shukitt-Hale et al. 2004, Wilson et al. 2004). The main functions affected by aging are speed of processing, working memory and the formation of long term episodic memories (Park et al. 2002). The impairment of spatial learning in aged rats is associated with changes in hippocampal connectivity and plasticity (Wilson et al. 2004). Recent evidence suggests that abnormal signal transduction is related to non-pathological memory impairment among aged rats (Brightwell et al. 2004). Also sensorimotor functions decline with age in rodents (Ingram 1988, Stoll et al. 1990, Briggs et al. 1999, Markowska 1999). Aged rats show significantly reduced agilities, mobility and deterioration in gait, particularly with hindlimbs. Compared with young adults, aged rats not only use digits and pads for locomotion, but also the more distal parts of the heels, which may lead to reduced altered stimulation of the hindlimb (Godde et al. 2002). Optical imaging revealed that the hindlimb presentations of aged rats were significantly reduced in size while the forelimb presentations were about the same shape and size as the adult rats (Godde et al. 2002).

2.2. PLASTICITY IN THE NORMAL BRAIN

2.2.1. Plasticity mechanisms

Plasticity is termed as the ability to make adaptive changes in the structure and function of the central nervous system (CNS) (Bloom 1985). Possible mechanisms underlying neuronal plasticity include taking over the function of the damaged area by other structures functionally homologous to the damaged area, synaptogenesis, dendritic arborisation, and activation of silent synaptic connections.

Brain plasticity involves changes in the number and density of synapses on dendrites (synaptogenesis), dendritic length, and synapse size (Greenough et al. 1994). Silent synapses are thought to be recruited in activity dependent plasticity (Nicoll and Malenka 1999). In addition, plastic changes are seen also in glial cells and the brain vasculature (Kolb 1995b). Long-term potentiation (LTP) may be an important mechanism underlying the plastic changes that occur during acquisition of new learning and memory. LTP is a rapid, brief sequence of excitatory pulses which enhance synaptic efficacy, lasting for hours by repeated stimulation (Bliss and Lomo 1973).

Moreover, recent data demonstrated that several intracellular signaling pathways such as mitogen-activated protein kinases, extracellular signal-regulated kinases, serine/threonine kinase protein kinase B and transcription factors such as adenosine 3',5'-cyclic monophosphate (cAMP) response element binding protein (CREB), delta-FosB, and proteins such as dopamine, cAMP-regulated phosphoprotein of 32,000 kDa were involved in neuronal plasticity (Wang et al. 2003, McClung et al. 2004, Nestler 2004, Thomas and Huganir 2004, Gould and Manji 2005). In addition, cAMP dependent protein kinase phosphorylation of the AMPA receptor subunits directly controls the synaptic incorporation of AMPA receptors which plays a critical role in synaptic plasticity (Esteban et al. 2003).

Contrary to early dogma, adult neurogenesis has been established as one possible mechanism of neural plasticity. Neural stem cells which exist throughout life can generate new neurons, astrocytes, and oligodendrocytes in specific regions of the adult mammalian brain, particularly in the olfactory systems, hippocampus and the subventricular zone (Gage 2002, Taupin and Gage 2002, van Praag et al. 2002, Kempermann et al. 2004).

2.2.2. Brain plasticity and aging

There is evidence to suggest that the aged brain exhibits increased vulnerability towards insults. The regenerative response of neurons and glial cells seems to be delayed or occurs at a diminished rate in aged rats (Whittemore et al. 1985, Popa-Wagner et al. 1999). The capacity of neurons to create new synapses following partial denervation in the brain of aged rats are less robust compared to that of younger rats (Cotman and Scheff 1979). 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 which suggests that the initial phases of synaptic replacement is retarded (Anderson et al. 1986). Factors that stimulate neurite outgrowth and upregulate growth associated protein-43 (GAP-43) mRNA, a growth associated protein and a molecular marker of axonal growth in response to a partial deafferentation lesion, diminish with age (Schauwecker et al. 1995). The upregulation of potentially restorative structural elements and increased levels of gene expression of neurofilament proteins are also preserved after focal cerebral ischemia, but diminished when compared to young animals (Popa-Wagner et al. 1999, Schroeder 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). A similar age-related decrease in plasticity has been demonstrated to occur in humans (Nakayama et al. 1994b, Pohjasvaara et al. 1997).

Interestingly, functional imaging studies have indicated that elderly subjects need to recruit

additional cortical and subcortical areas even for the performance of a simple motor task (Mattay et al. 2002). These changes may represent compensatory mechanisms evoked by the aging brain, such as reorganization and redistribution of functional networks. In addition, the cutaneous receptive fields of the hindpaw representations in somatosensory cortex and the cortical areas excited by tactile point-stimulation are enlarged and highly overlapping in old rats when compared to young rats (Spengler et al. 1995). The topographic changes in both aged human and rat brain may be a consequence of age-related structural loss in the cerebral cortex.

2.3. BRAIN PLASTICITY AFTER STROKE

Resolution of edema, establishment of collateral flow, amelioration of inflammation all contribute to the initial improvements in neurological function occuring during the acute stage of stroke. This is followed by complex plastic alterations within specific time windows in areas adjacent to the infarct but also in the contralateral hemisphere which attempt to compensate for the lost functions.

2.3.1. Altered excitatory and inhibitory neurotransmission

Removal of local inhibition could provide one mechanism for cortical reorganisation by unmasking latent excitatory horizontal connections (Jacobs and Donoghue 1991). There is increasing evidence indicating that an ischemic brain lesion leads to reduced inhibitory activity and hyperexcitability. LTP induction is facilitated in the vicinity of the cortical infarction (Hagemann et al. 1998). Also the contralateral hemisphere shows hyperexcitability and this is not restricted to brain areas homotopic to the lesion. There is an imbalance between excitatory and inhibitory neurotransmission, resulting in local hyperexcitability (Mittmann et al. 1998); NMDA receptors are up-regulated whereas the $GABA_A$ receptors are down-regulated in the ipsi- and contralateral neocortex after focal cerebral ischemia (Qu et al. 1998b). 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 encourage excitability after a lesion such as after stroke and thereby facilitate synaptic strengthening. Changes in inhibitory activity seem to be tightly coupled to functional recovery. Diazepam, a GABA receptor agonist, delays recovery, when given acutely after frontal cortex lesions in rats (Schallert et al. 1986), whereas pentylenetetrazol, a GABA receptor antagonist, is claimed to accelerate recovery after sensorimotor lesions in rats (Hernandez and Schallert 1988).

2.3.2. Diaschisis

The term diaschisis means functional impairments in remote regions that are connected to the infarcted area (von Monakow 1924). It has been suggested that resolution of diaschisis contributes to recovery (Feeney and Baron 1986) and that the extent of diaschisis determines the degree of functional impairment (Donnan et al. 1991). However, single photon emission computed tomography (SPECT) measurements have shown that clinical recovery is not accompanied by resolution of remote effects (Bowler et al. 1995). Thus, diaschisis may persist for a long time after a significant recovery has occurred (Infeld et al. 1995). Moreover, under certain conditions diaschisis may represent a loss of remote inhibition rather than a loss of remote facilitation, as von Monakow originally suggested (Andrews 1991).

2.3.3. Neuronal sprouting

Local growth of axons and synapses could provide a mechanism for intracortical remapping following brain injury. 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 the rat after experimental stroke (Stroemer et al. 1995, Rowntree and Kolb 1997, Stroemer et al. 1998). Sprouting can also occur remote from the site of damage even in the undamaged hemisphere. Neither a lesion nor asymmetrical limb use alone could account for the dendritic

sprouting in the intact hemisphere, lesion-behavior interactions may contribute to this process (Jones and Schallert 1994). Sprouting is tightly coupled to functional recovery following brain injury in rats.

2.3.4. Reorganization

During recent years, it has become clear that adult brain maintains the ability to undergo extensive reorganization (Dijkhuizen et al. 2001, Bütefisch et al. 2003, Dijkhuizen et al. 2003, Rossini and Dal Forno 2004, Ward 2004, Hanlon et al. 2005).

Reorganization can occur in regions adjacent to the lesion, in remote undamaged areas of the lesioned hemisphere, or in areas in the intact hemisphere. Following a focal lesion in the brain region controlling movements of one hand of squirrel monkey, the cortical areas adjacent to the injury undergo 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 occuring 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 local remapping in humans (Weiller et al. 1993). Plasticity can also occur in the remote undamaged areas of the lesioned hemisphere, with intact brain regions taking over the lost function of the damaged cortex (Frost et al. 2003). This is made possible by the existence of multiple representation areas in the CNS. There are clinical reports of patients who have suffered a second stroke (Fisher 1992, Lee and van Donkelaar 1995) and many functional imaging studies showing increased activation of the ipsilateral motor areas after stroke (Caramia et al. 1996, Cramer et al. 1997, Honda et al. 1997, Netz et al. 1997, Cao et al. 1998, Cuadrado et al. 1999) which provide evidence that the recovery can also be mediated by changes in the undamaged hemisphere.

2.3.5. Behavioral compensation

A certain amount of recovery can be achieved through behavioural compensation rather than a true reinstitution of function. Several studies have shown that compensatory movement strategies come into the play after brain injury in humans (Kolb 1995a) and animals (Whishaw et al. 1991, Friel and Nudo 1998, Whishaw 2000). Kolb has given an example of this from his own life after losing vision in 1/4 of the foveal representation in the left eye (Kolb 1995a). He learned to fixate his vision in a way that the blind spot did not disturb recognition. Similarly, animals can learn to use compensatory motor strategies, or tricks when sustaining an injury (Jones and Schallert 1994, Schallert et al. 2000a). This means that the validity of behavioral tests and their interpretation becomes a key issue in recovery studies. Using classic behavioral methods, it is often difficult to disentangle true functional recovery from learned motor compensation (Schallert 1988, Whishaw 2000, Schallert et al. 2000b,c). In addition, compensatory tricks may explain some of the apparently drug related improvements in function following brain insults (Schallert et al. 2003).

2.4. DRUG TREATMENT AND BRAIN PLASTICITY AND RECOVERY

The recovering brain remains sensitive to drug treatment and other manipulations. 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 (Feeney et al. 1982, Crisostomo et al. 1988, Walker-Batson et al. 1995) (Table 1). These observations also suggest that relatively rapid drug-induced physiological changes can contribute to a long-lasting functional reorganization.

Table 1. Effect of selected CNS-active drug on functional recovery.

Drug	Action	Effect
Sympathomimetic amines and related drugs		
Amphetamine		+
Phenylpropanolamine	Sympathomimetic	+
Methylphenidate	Sympathomimetic	+
GABAergic drugs		
Diazepam	GABA agonist	-
Muscimol	GABA agonist	-
Phenobarbital		-
Phenytoin		-
Antidepressants		
Trazodone	Serotonin reuptake blocker	-
Fluoxetine	Serotonin reuptake blocker	+/-
Amitriptyline	Serotonin/norepinephrine reuptake blocker	- or +/-
Desipramine	Norepinephrine reuptake blocker	+
Neuroleptics		
Haloperidol	Butyrophenone, dopamine antagonist	-
Fluanisone	Butyrophenone	-
Droperidol	Butyrophenone	-
Spiroperidol	Dopamine antagonist	-
Apomorphine	Dopamine agonist	+
Cholinergic drugs		
YM796	Muscarinic agonist	+
Scopolamine	Muscarinic antagonist	-

+ indicates a beneficial effect on recovery; - indicates a detrimental effect; and +/- indicates neutral effects on recovery. Modified from (Goldstein 1993, Yamaguchi et al. 1995, Goldstein 1998)

2.4.1. Mechanisms of drug induced behavioral alterations

Drugs can affect functional recovery by enhancing or impairing the brain plasticity processes. Drugs that worsen diaschisis would be anticipated to be detrimental whereas those that promote the resolution of diaschisis would be beneficial. However, the role of diaschisis in recovery is challenged by clinical observations that improvement in crossed cerebellar diaschisis does not correlate with recovery after stroke affecting the cerebral hemisphere (Infeld et al. 1995). A second mechanism of action is based on relearning process related to

LTP, the putative cellular mechanism of learning and memory. Neurotransmitters such as dopamine (Otani et al. 2003), serotonin (Ohashi et al. 2003, Matsumoto et al. 2004) and GABA (Douglas et al. 1983, 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 determine whether corticostriatal LTP or long term depression (LTD) is 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, Dietrich et al. 1990). Drug induced neurogenesis may also contribute to the recovery process (Santarelli et al. 2003, Castren 2004).

2.4.2. Sympathomimetics and related drugs

Amphetamine modulates a variety of neurotransmitter systems in the brain (West et al. 1995, Cardenas et al. 2004). Administration of amphetamine has been reported to enhance recovery after brain injury including middle cerebral artery occlusion and trauma in both experimental animals and humans (Feeney et al. 1982, Feeney and Hovda 1985, Crisostomo et al. 1988, Sutton et al. 1989, Hurwitz et al. 1991, Stroemer et al. 1993, Walker-Batson et al. 1995, Hornstein et al. 1996, Dhillon et al. 1998, Walker-Batson et al. 2001, Martinsson and Eksborg 2004). Amphetamine is thought to act through the noradrenergic system (Boyeson and Feeney 1990, Boyeson et al. 1992a,b, Boyeson et al. 1994, Goldstein 1997).

Reorganization, especially in the cerebral hemisphere contralateral to a cortical injury may also contribute to the effects of amphetamine (Stroemer et al. 1998). In addition, amphetamine treatment after focal ischemia has been found to promote alternate circuit activation which allows normally depressed circuits to respond to sensory stimulation in the normal and infarcted rat (Dietrich et al. 1990).

If enhanced noradrenergic activity does contribute to the beneficial action of amphetamine following brain injury, other drugs that increase norepinephrine release or decrease its

metabolism would be expected to be beneficial. Centrally acting α_2-adrenergic receptor antagonists (*e.g.*, yohimbine, idazoxan, atipamezole), which increase the release of norepinephrine, have been shown to facilitate recovery after cortical lesions (Goldstein 1989, Sutton and Feeney 1992) or after middle cerebral artery occlusion (Jolkkonen et al. 2000a, Butovas et al. 2001, Puurunen et al. 2001, Barbelivien et al. 2002). In contrast, α_1-adrenergic receptor antagonists (*e.g.*, prazosin) or α_2-adrenergic receptor agonists (*e.g.*, clonidine) which decrease noradrenergic activity in the brain have been shown to retard the recovery and transiently reinstate the symptoms after recovery has occurred (Feeney and Westerberg 1990, Goldstein and Davis 1990, Sutton and Feeney 1992).

2.4.3. Neuroleptics

The typical neuroleptic, haloperidol, which is a dopamine receptor antagonist and potential noradrenergic receptor blocker (Davis et al. 1978, Cohen and Lipinski 1986, Fang and Yu 1995) is considered to be harmful to the motor recovery in stroke patients (Goldstein 1993) and experimental models (Feeney et al. 1982, Hovda and Feeney 1985, Feeney and Westerberg 1990). The detrimental effect of haloperidol may be partially due to dopamine receptor blockade in striatum resulting in extrapyramidal motor symptoms (Kapur et al. 2000, 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).

The effects of new atypical neuroleptic such as risperidone on possible cerebrovascular events remain controversial (Wooltorton 2002, Bobo and More 2003, Herrmann et al. 2004, Smith and Beier 2004). It was found that 4% of risperidone-treated dementia patients suffered cerebrovascular adverse events compared with 2% of placebo-treated patients (Wooltorton 2002). However, 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. Olanzapine and risperidone did not demonstrate any significant increase in the stroke risk of stroke compared to typical neuroleptics (Herrmann et al. 2004). It should be noted that in this study cerebrovascular events other than stroke (*e.g.,* transient ischemic attacks, mild strokes) were not included, which may have led to an underestimation of the risks associated with these agents.

In addition, there is evidence showing that both typical and atypical neuroleptics can regulate synaptic 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 D_1 and glutamate NMDA receptors is required for eliciting the long-term changes associated with plasticity (Cragg 2003, Gemperle et al. 2003, Centonze et al. 2004, Hjelmstad 2004, Meltzer 2004, Chen and Chen 2005).

2.4.4. Antidepressants

Antidepressants alter synaptic concentrations of catecholamines and thus promote possibly the recovery of function. 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 hours after injury transiently impaired motor recovery. A reinjection of trazodone reinstated the hemiparesis for up to 6 hours 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). Data with fluoxetine are variable with beneficial or no significant effect on the recovery process being reported (Boyeson et al. 1994, Dam et al. 1996, Jolkkonen et al. 2000b, Wilson and Hamm 2002).

More importantly, recent data indicated that antidepressants are involved in the signal pathway of neurotrophins and CREB. Furthermore, chronic antidepressant treatments increase adult hippocampal neurogenesis whereas disrupting antidepressant-induced neurogenesis can block the behavioral responses to these drugs (Santarelli et al. 2003, Castren 2004). However, the latest study challenge 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 causing neurogenesis (Sairanen et al. 2005).

2.4.5. 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 (Schallert et al. 1986, Hernandez and Holling 1994). 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). The effects of GABAergic system on recovery after brain damage are likely to be due to the major inhibitory action of this system (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 the cortical reorganization (Jacobs and Donoghue 1991). One should note that GABA receptor agonists are 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.

2.4.6. Cholinergic drugs

The cholinergic system is involved in brain excitability and has an important role in attention and arousal (Wenk 1997, Brown and Marsden 1998). 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 necessary for learning (Conner et al. 2003). Furthermore, a recent study has indicated that adult neurogenesis is regulated by the cholinergic system. A selective lesion of the basal forebrain decrease the number of cholinergic cells colocalized with bromodeoxyuridine and the neuronal nuclei marker NeuN in the granule cell layers of the dentate gyrus and olfactory bulb (Cooper-Kuhn et al. 2004). More interestingly, the basal forebrain cholinergic system is thought to be involved in nerve growth factor induced augmented whisker functional representation of adult rats (Prakash et al. 2004). Thus, it is surprising that cholinergic drugs have not been studied with respect to recovery. There is only scattered evidence that administration of acetylcholine may enhance recovery of function (Feeney and Sutton 1987) and anticholinergic drugs, such as scopolamine, may interfere with recovery (De Ryck et al. 1990).

2.4.7. Others

Recent evidence on brain plasticity has prompted increasing interest in possible recovery enhancing drugs. For example, growth factors such as fibroblast growth factors have been reported to be promising agents, being attribute to enhance axonal plasticity and functional recovery following stroke in rodents (Kawamata et al. 1997, Chen et al. 2002). The recovery enhancing effect of basic fibroblast growth factor may involve stimulation of neuronal sprouting in the intact brain as GAP-43 immunoreactivity in the cortex contralateral to cerebral infarct is elevated. Similarly, in adult rats with unilateral cortical infarct, inosine increased GAP-43 immunoreactivity in the crossed corticospinal tract fibers. This suggests that inosine had been stimulating neurons in the undamaged brain areas to grow new projections to the damaged areas which in turn improved behavioral outcome. Recent data

also show that myelin might be a primary inhibitor of axonal growth in the adult brain. Nogo-A is one of the neurite inhibitory proteins (Chen et al. 2000, GrandPre et al. 2000, Prinjha et al. 2000) which mediates its action through the specific receptor molecule, Nogo-66 receptor (Fournier et al. 2001). Blockade of Nogo-A with the monoclonal antibodies has improved functional recovery in different experimental stroke models (Papadopoulos et al. 2002, Wiessner et al. 2003). Treatment with a purified monoclonal anti-Nogo-A antibody (7B12) in both photothrombotic and permanent middle cerebral artery occlusion models significantly increased the midline crossing corticospinal fibers originating in the unlesioned sensorimotor cortex correlated and this was associated with improved behavioral outcome evaluated by forepaw function without influencing infarct volume (Wiessner et al. 2003).

2.5. PSYCHOTROPIC MEDICATION AND AGING

Age at the time of brain injury is generally considered to be an important determinant of functional recovery. The older patients show less recovery (Nakayama et al. 1994b, Pohjasvaara et al. 1997). However, recent data have challenged this common belief (Davis et al. 1995, Popa-Wagner et al. 1999, Kharlamov et al. 2000, Shapira et al. 2002) and suggest plastic capacity is also possible in aged subjects.

The number of elderly people will increase dramatically in next few years. Many of them are prescribed with CNS drugs such as antidepressants, neuroleptics, and hypnotics for the purpose of primary care and treatment of behavioral disturbances related to dementia (Elmstahl et al. 1998, Lasser and Sunderland 1998, Margallo-Lana et al. 2001, Linjakumpu et al. 2002a). On a global basis the elderly use psychotropics more frequently than the general population except in the very oldest age groups (Ohayon et al. 1998, Blazer et al. 2000, Hartikainen et al. 2003a,b). Finnish studies have revealed that both men and women aged 75 years or over use anxiolytics, sleeping pills, antipsychotics, and antidepressants more commonly than the other age groups (Klaukka 2000, Hartikainen et al. 2003a,b, Hartikainen

and Klaukka 2004) (Fig. 1).

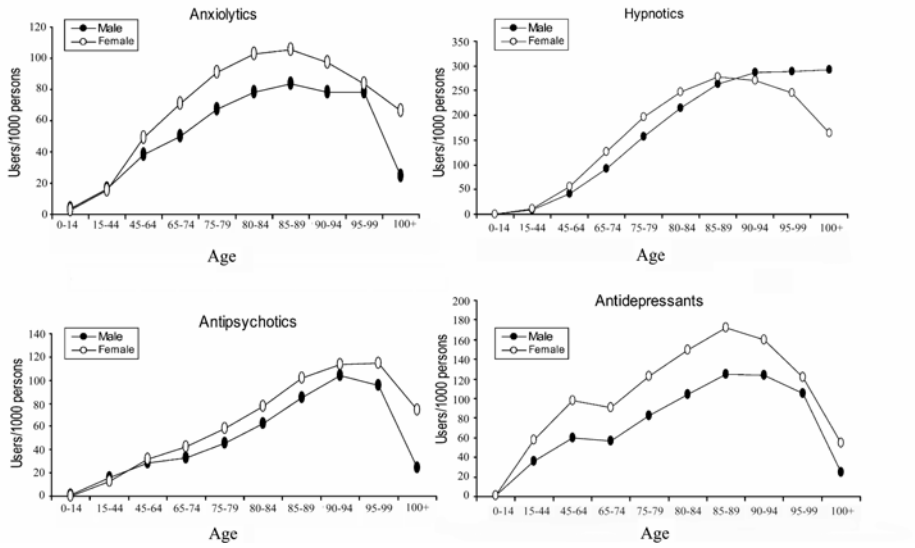

Fig. 1. CNS-active drugs use in the Finnish elderly (from Hartikainen and Klaukka 2004).

As much as 20-53% of the elderly population are reported to be taking neuroleptic medication including the atypical neuroleptic, risperidone, to control delusions, aggression, and anxiety (Lasser and Sunderland 1998, Ruths et al. 2001, Sorensen et al. 2001). The use of antidepressants is also common among elderly individuals. It has been reported that somewhere between 14-61% of the elderly population are being prescribed with antidepressant medications in particular, selective serotonin reuptake inhibitors such as fluoxetine (Skoog et al. 1993, Lasser and Sunderland 1998, Ruths et al. 2001, Sorensen et al. 2001).

Polypharmacy is common in the elderly (Elmstahl et al. 1998, Weiner et al. 1998, Linjakumpu et al. 2002a,b). The use of two or more CNS-active drugs concominantly is related to an increased risk of accidents compared to the use of one drug alone (Weiner et al. 1998). Polypharmacy increases the possibility of unexpected interactions and adverse effects (Tune et al. 1992, Barat et al. 2000) due to age-related changes in pharmacokinetics and

pharmacodynamics, and the decline in neuronal number and function (Hughes 1998, Pollock 1998). Pharmacokinetic alterations may also be caused by changes in absorption, distribution, or elimination via metabolism in the liver and/or in excretion by the kidneys.

Increasing amounts of new psychotropic medicines are being prescribed without knowing any deep understanding of their effects on possible cerebrovascular events or recovery after a stroke. The recent evidence that risperidone might increase the rate of cerebrovascular events is a good example of one such unexpected adverse effect. Both experimental and clinical studies are needed to explore the safety of psychotropic medication more thoroughly.

3. AIMS OF THE STUDY

The purpose of the present thesis was to investigate the effects of psychotropic medications on the histological and functional outcome following cortical photothrombosis in aged rats. This was an experimental analogue to clinical practice in which elderly patients, who have sustained small focal stroke or who are at high risk of stroke, are treated with medication to control dementia, mood, aggression and other behavioral problems. The specific aims are:

1) To investigate the effect of galanthamine, a selective competitive cholinesterase inhibitor, on the histological and functional outcome following cortical photothrombosis in young and aged rats (**II**).

2) To investigate long-term administration of risperidone, an atypical neuroleptic, alone or in combination with fluoxetine, a selective serotonin reuptake inhibitor, on histological and functional outcome in aged rats subjected to cortical stroke (**I, III**).

3) To investigate the effect of zopiclone, a hypnotic drug, on histological and functional outcome after cortical stroke in aged rats (**IV**). In addition, possible reinstatement of the behavioral deficit by a single dose of zopiclone was studied after a washout period.

4. MATERIALS AND METHODS

4.1. Animals

Male Wistar rats (National Laboratory Animal Centre, Kuopio, 5 months, 385–503 g; 24 months, 424–744 g) were used in the present study. The animals had free access to food and water and were housed in individual cages in a temperature-controlled environment (20±1 °C) with lights on from 7.00 to 19.00 h. Experimental procedures were conducted in accordance with the European Community Council directives 86/609/EEC and the study was approved by the Ethics Committee of the University of Kuopio and the Provincial Government of Kuopio.

4.2. Drug administration

Galanthamine (Tocris, UK) was dissolved in 0.9% NaCl and administered at a dose of 2.5 mg/kg (i.p., once a day) beginning 4 days before ischemia induction, with treatment continuing for 25 days (**II**). The drug was administered 2 hours before the behavioral tests or surgery. The dose (2.5 mg/kg) was selected based on previous studies (Mihailova and Yamboliev 1986, Bickel et al. 1991, Monbaliu et al. 2003) to produce plasma levels relevant to the patient situation. The ischemic control rats and sham-operated rats were given an equivalent volume of 0.9% NaCl.

Risperidone (Kemprotec, UK) was dissolved in dilute acid solution and administered at a dose of 1 mg/kg (i.p., once a day) and fluoxetine (Kemprotec, UK) was dissolved in 0.9% NaCl and administered at a dose of 5 mg/kg (i.p., once a day) beginning 7 days before ischemia induction and continuing for 28 days (**I, III**). On the operation day, the drugs were administered 2 hours before surgery. The doses were selected based on a pilot study and previous reports (Durand et al. 1999, To et al. 1999, Jolkkonen et al. 2000b, Shirazi-Southall et al. 2002, Kapur et al. 2003). Ischemic control rats and sham-operated rats were given an equivalent volume of vehicle.

Zopiclone (Orion Corporation, Orion Pharma, Finland) was dissolved in dimethyl sulfoxide and administered at a dose of 3 mg/kg (i.p., once a day) beginning 4 days before ischemia induction and continuing for 23 days (**IV**). The zopiclone dose was selected based on a pilot study and previous reports (Longo et al. 1988, Yamamoto et al. 1989, Cohen and Sanger 1994, Gauthier et al. 1997). The ischemic control rats and sham-operated rats were given an equivalent volume of vehicle. After a 7 day washout period, the rats were administered a single dose of zopiclone and then retested. The drug was administered 2 hours before surgery and 24 hours before behavioral tests.

4.3. Cortical photothrombosis

The cortical photothrombotic stroke model was first described by Watson et al. (1985). Photochemical reaction leads to peroxidation of membrane lipids and vascular endothelium damage, which faciliate platelet adhesion and aggregation to the point of vascular occlusion (Fig. 2). Rose Bengal, one of the Type II dyes (Spikes 1989) is photoactivated primarily in small cortical vessels (diameter <50 μm), which are concentrated mainly at the pial surface. The resulting lowest triplet state of the sensitizer molecule donates its electronic energy directly to molecular oxygen to generate singlet oxygen which is not a free radical because of absence of the unpaired electrons. A secondary chain process of peroxidation, which causes microrupture of endothelial cell membranes followed by end-arterial occlusive platelet aggregation, can occur in the case of unsaturated fatty acids. The subsequent formation of a non-fibrin containing thrombus formation and vascular stasis result in vasogenic edema that is sufficiently severe to occlude the deeper cortical vasculature by mechanical compression. This compression augments the depth and volume of evolving infarction, ultimately resulting in focal cerebral infarction and subsequent necrosis. The penumbral area surrounding the core of infarction is small compared with that produced by other arterial occlusion models.

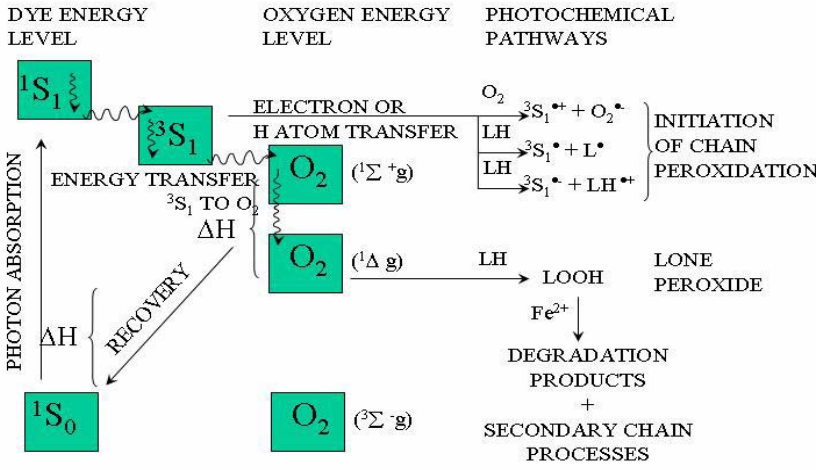

Fig. 2. Mechanisms of photochemical reaction (modified from Watson 1998).

In the present work, cortical photothrombosis was induced by focusing light to the sensorimotor cortex in Rose Bengal treated rats (Watson et al. 1985). Briefly, the rats were anesthetized with 5% halothane in 30% O_2/70% N_2O and placed in a stereotaxic frame. The anesthesia was maintained through the operation with 1–2% halothane delivered by a nose mask and the body temperature was kept at 37 °C by a rectal probe and heating pad. The skull was exposed and a cold white light (Olympus, Denmark) with a 4 mm aperture was positioned onto the skull 0.5 mm anterior to bregma and 3.7 mm lateral to the midline over the right motor cortex. The photochemical dye Rose Bengal (Sigma) was infused into the saphenous vein via a microinjection pump within 2 min (20 mg/kg), after which the light was turned on for 10 min. Skull surface temperature was monitored with a probe placed between the skull and the light source, and kept constant by cool airflow. Sham-operated animals were treated similarly but the light was not turned on. The rats were removed from the frame, sutured, and allowed to wake up in an incubator (32 °C) before being returned to their home cages.

4.4. Tapered/ledged beam-walking test

Sensorimotor functions of forelimbs and hindlimbs were tested using a tapered/ledged beam (Fig. 3). The rats were pretrained for 3 days to traverse the beam before ischemia induction. The animals were tested before surgery, and during the acute and chronic phases after operation. The beam-walking apparatus consisted of a tapered beam with underhanging ledges on each side to permit foot faults without falling. The end of the beam was connected to a black box (20.5 cm × 25 cm × 25 cm) with a platform at the starting point. A bright light was placed above the start point to motivate the rats to traverse the beam. The performance of the rats was videotaped and later analyzed by calculating the slip ratio of the impaired (contralateral to lesion) forelimb and hindlimb (number of slips/number of total steps) (Schallert et al. 2002, Schallert and Woodlee 2005). 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 mean of three trials was used for statistical analyses. All behavioral analysis was carried out by an observer blind to the experimental groups.

Fig. 3. Tapered/ledged beam-walking test.

4.5. Water-maze test

Spatial learning was analyzed with a match-to-place version of the Morris water-maze (Morris et al. 1982, Schallert et al. 1992, Troy Harker and Whishaw 2002). The animals were tested before ischemia induction, and during the acute and chronic phases after the operation

(**II, III**) except in the study **IV**, where rats were tested on postoperative days 17-19 and postoperative day 28 after a drug washout period in order to evaluate the acute effect of zopiclone.

The water-maze apparatus consisted of a circular, black fiberglass pool (150 cm in diameter, 74 cm deep, filled with water at 20 °C to a height of 54 cm). The top surface of the platform (10 cm × 10 cm, composed of black rubber) was 2.0 cm below the water line. The starting locations were called north, south, east and west, and were located arbitrarily at equal distances from each other on the pool rim. The swim paths were monitored by a video camera connected to a computer through an image analyzer (HVS image). If the rat failed to find the hidden platform within 70 s, it was placed on it. The rat was allowed to remain on the platform for 10 s. The inter-trial interval was 30–60 s. The rats were given four trials each day. Trials 1 and 3 began from one of the points located farthest from the platform and the start point was changed after each trial. The location of the platform was changed to a different quadrant each day. The escape latency (time to reach the platform) and the length of the path that the animal swam to find the platform were used to assess acquisition of the water-maze task. Swimming speed (path length/escape latency) was used to assess the motor activity of rats. At the end of the testing period, a probe trial of 30 s without the platform was used to assess how well the rats remembered the location of the platform (number of passes over the previous platform location and time spent in the target quadrant). Additional young (n = 10) and aged (n = 10) *naive* animals were tested with a visible platform in order to evaluate the possibility that age-related decline in recognition ability or escape motivation would affect the water-maze performance (**II**). All animals were also tested with a visible platform at the end of the follow-up (postoperative day 19) (**III**).

4.6. Histology

The animals were decapitated at the end of the follow-up and the brains were rapidly removed from the skulls and frozen in cold isopentane kept on dry ice. Coronal sections (40 μm) were cut through the brain on a cryostat and sections at 0.4-mm intervals were collected on gelatinized slides. Sections were stained for 20 min with a solution containing 1.2 mmol/l nitroblue tetrazolium (NBT) and 0.1 mol/l sodium succinate in 0.1 mol/l sodium phosphate buffer, pH 7.6, at 37 °C (Nachlas et al. 1957). The sections were then rinsed in water, dehydrated in an ascending series of alcohol baths, cleared in xylenes, and coverslipped with Depex. Estimations of the infarct areas from NBT-stained sections were performed using an image analysis system (MCID). The image of each section was stored as a 1280 × 1024 matrix of calibrated pixel units. The digitized image was then displayed on a video screen and the cortical infarct was outlined. Total infarct volumes were calculated by multiplying the infarct area by the distance between the sections and summing together the volumes for each individual brain.

4.7. Statistics

Beam-walking data for the overall group effect were analyzed using ANOVA for repeated measures. Comparisons between groups were made using one-way ANOVA with Tukey's post hoc test or *t* tests for independent samples. Water-maze data (path length, escape latency, swimming speed) were analyzed using ANOVA for repeated measures (**II, IV**). When the interaction effect was significant, comparisons between groups were studied using paired *t* tests with Bonferroni corrections. Statistical differences between groups in the number of passes over the removed platform (probe trial) were analyzed using one-way ANOVA with Duncan’s post hoc test. Since risperidone and the combination of fluoxetine and risperidone affected the swimming speed of rats, water-maze data were analyzed using linear mixed models for repeated measures using swimming speed as a time dependent covariate (Brown and Prescott 1999) (**III**). The F-test denominator degrees of freedom are rounded

Sattethwithe's approximations appropriate for the repeated measures analysis using mixed models framework. Bonferroni's post hoc test was used for pairwise comparisons, when needed. Statistical differences between groups in the number of passes over the removed platform and time spent in the quadrant that the platform was located (probe trial), and percentage of time spent in equal-size zones of the water maze pool were analyzed using analysis of variance with swimming speed as a covariate followed by Tukey's post hoc test. Statistical differences between groups in infarct volumes in the cortex were analyzed using one-way ANOVA with Tukey's post hoc test.

5. RESULTS

5.1. Survival of rats

The cortical photothrombosis was characterized by a low mortality (n=3) and a low number of post-operative complications affecting behavioral performance (n=5). There were no significant differences in body weights between sham-operated and ischemic control rats also highlighting the noninvasive nature of the operation.

5.2. Histological findings

The cortical infarct was typically located in the frontal cortex (Fr1 and Fr2) and extended to the corpus callosum with no evidence of striatal damage (Paxinos and Watson 1998). It mainly affected the hindlimb region, but in some cases the forelimb region was also affected (Fig. 4). Resolution of necrotic tissue resulted in the formation of a partially fluid-filled cyst by the end of the follow-up. The infarct volumes were 9.8±0.6 mm^3 (n=82). Three rats with no detectable cortical lesion were excluded.

Fig. 4. Coronal sections showing typical cortical infarct.

There was a significant age effect (P=0.004) in infarct volumes for young ischemic controls (15.4±0.9 mm^3) and for aged ischemic controls (11.7±1.1 mm^3). Galanthamine, fluoxetine, risperidone, combination of fluoxetine and risperidone, or zopiclone did not affect infarct volumes in the cortex.

5.3. Behavioral outcome following cortical photothrombosis

5.3.1. Effect of age (II)

Cortical infarct by photothrombosis caused a significant chronic hindlimb impairment and transient forelimb impairment in rats. Slip ratios with the hindlimb were higher compared to those with the forelimb, due to the wider base. Unilateral photochemical lesion did not induce any detectable cognitive impairment.

We found that the slip ratio with both forelimb and hindlimb was 2-3 times higher in aged compared with young rats (sham-operated only). Focal cortical photothrombosis caused a transient impairment in forelimb function and a permanent impairment in hindlimb function in both age groups. The similar recovery from impairment in young and aged rats following cortical photothrombosis suggests that aged rats are not more vulnerable to motor impairment.

Despite use of a more sensitive Morris water maze test design, even aged rats learned the task by the end of the follow-up. Escape latencies of aged rats were, however, longer compared to those of young rats. In the additional study using a visible platform, it was found that the aged rats needed more time to escape onto the visible platform and their swim paths were longer. A unilateral cortical lesion did not cause any detectable spatial learning impairment in young rats or in aged rats.

5.3.2. Effect of galanthamine (II)

Galanthamine did not worsen the beam-walking performances in young or aged rats (Fig. 5).

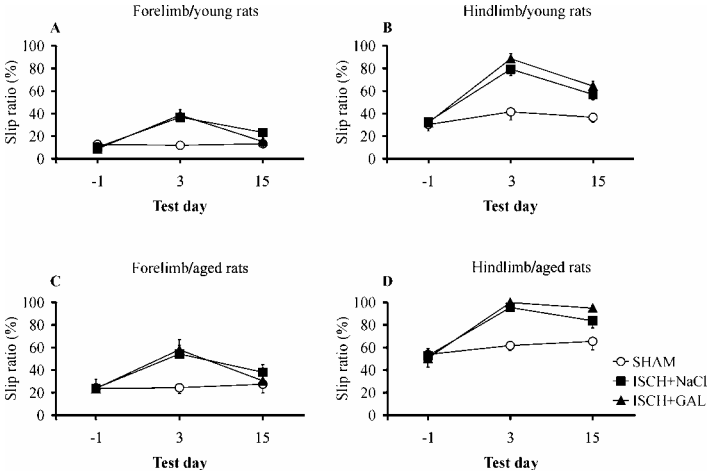

Fig. 5. Slip ratios in the beam-walking test for young and aged rats subjected to cortical photothrombosis and treated with galanthamine.

There were no significant differences in length of path, escape latency, or swim speed in ischemic young or aged rats treated with galanthamine compared with other rats (Fig. 6).

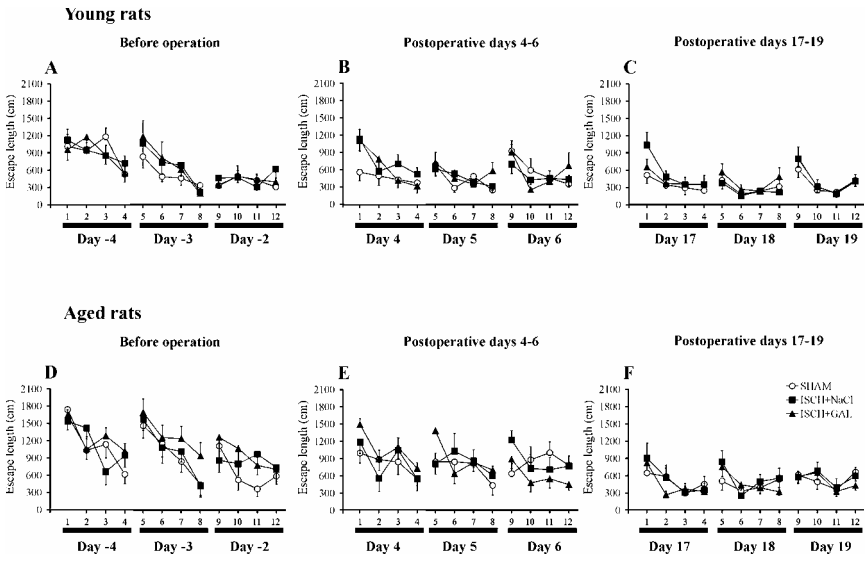

Fig. 6. Escape length in the water maze test for young and aged rats subjected to cortical photothrombosis and treated with galanthamine.

5.3.3. Effect of risperidone and/or fluoxetine (I, III)

Two hours after drug administration, ischemic rats treated with risperidone and ischemic rats treated with a combination of risperidone and fluoxetine made more slips with impaired hindlimb than ischemic control rats. The significant group effect in slip ratio with the hindlimb disappeared when the rats were tested 24 hours after drug administration. There was no significant difference in slip ratios with the impaired hindlimb between the ischemic controls and ischemic rats treated with fluoxetine. Risperidone, fluoxetine, and combination of risperidone and fluoxetine did not affect slip ratios for the contralateral forelimb (Fig. 7).

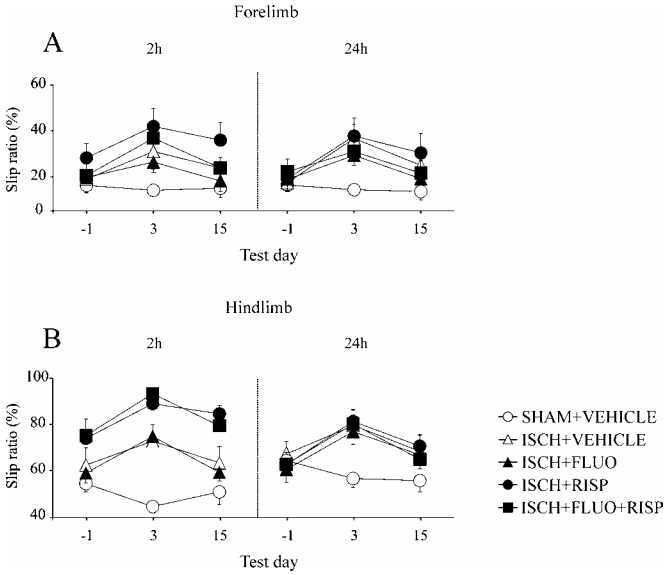

Fig. 7. Slip ratios in the beam-walking test for aged rats subjected to cortical photothrombosis and treated with risperidone and/or fluoxetine.

Water-maze performance was impaired 2 hours after administration of risperidone or the combination of risperidone and fluoxetine both in the hidden platform task and the visible platform task. Fluoxetine did not affect water-maze performance (Fig. 8).

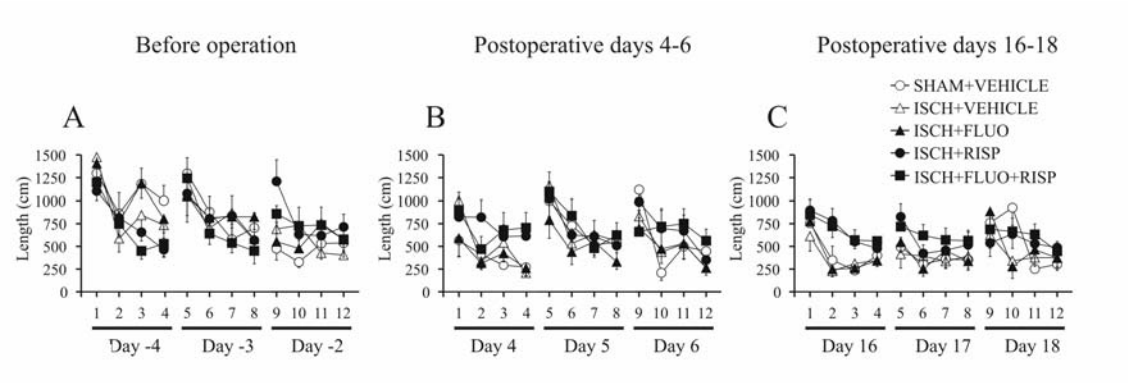

Fig. 8. Escape length in the water maze test for aged rats subjected to cortical photothrombosis and treated with risperidone and/or fluoxetine.

5.3.4. Effect of zopiclone (IV)

Beam-walking data showed that ischemic rats treated with zopiclone were not more impaired than untreated rats. There was no significant difference in slip ratio with the impaired hindlimb between the ischemic controls and ischemic rats treated with zopiclone. Indeed, zopiclone treated rats showed fewer faults with the impaired hindlimb than ischemic controls on postoperative day 16. There was no significant group effect in slip ratios for the contralateral forelimb and there was no significant group effect in slip ratio with the ipsilateral forelimb or hindlimb. After the washout period a single dose of zopiclone did not worsen forelimb or hindlimb function. There was no significant group effect in the number of slips made with the ipsilateral forelimb or hindlimb after the washout period (Fig. 9).

Water-maze performance was not affected by zopiclone before the washout period. Compared with the ischemic controls, ischemic rats treated with zopiclone exhibited a shorter escape length, and escape latency after the washout period (Fig. 10).

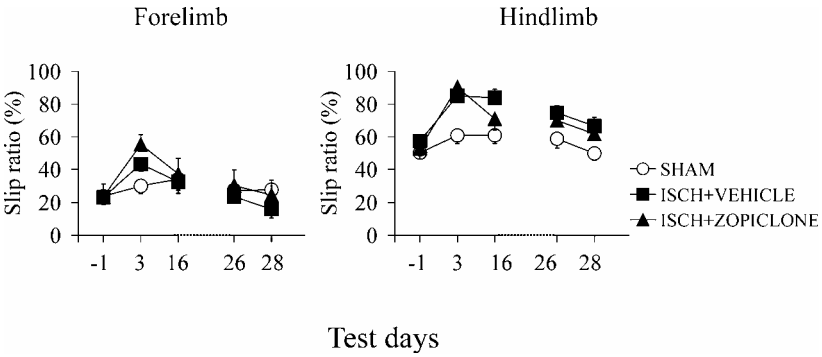

Fig. 9. Slip ratios in the beam-walking test for aged rats subjected to cortical photothrombosis and treated with zopiclone.

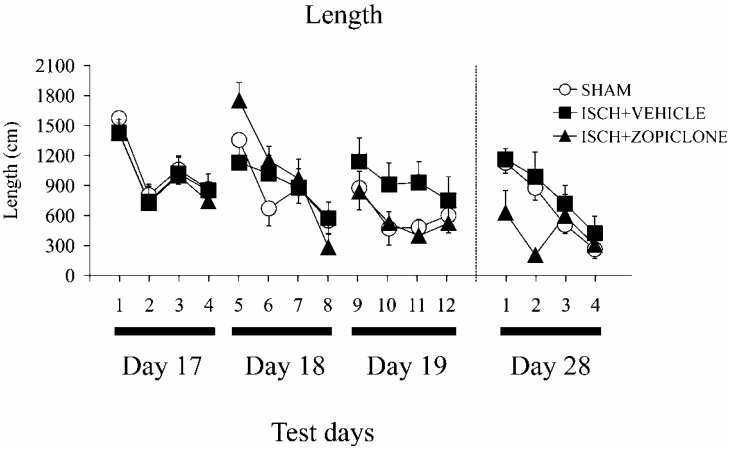

Fig. 10. Escape length in the water maze test for aged rats subjected to cortical photothrombosis and treated with zopiclone.

6. DISCUSSION

6.1. Methodological considerations

Although stroke is strongly associated with age, most data are typically obtained from experiments in young animals. This is despite the recommendation by the STAIR committee (STAIR 1999) and the more recent Stroke Progress Review Group that data in aged animals might be considered as more appropriate from a preclinical standpoint than that obtained from the young adults. The direct comparison of young and aged animals is, however, complicated as also shown in the present study (**II**). Because of age-related differences (*e.g.,* in the body weight, visual acuity, or motivation), the behavioral data were not directly compared statistically. In addition, increased skull thickness by 10–20% in aged rats was noted, which may have contributed to the difference in infarct size. The use of aged rats is usually limited because of their high price and for that reason in the present study only a single drug dose was selected for testing with a relatively small group size.

We used a photosensitive dye (Rose Bengal) and focused light as the means produce cortical infarct, because the operation is noninvasive and mortality is low, the cortical lesion produced is consistent, and the lesion has a precise location and size. The degree to which the Rose Bengal model is useful preclinically for evaluating drug effects remains unclear. One specific feature of the Rose Bengal is the relatively restricted penumbral area, because of the end arterial occlusion produced and the massive vasogenic edema. There is, however, pharmacological evidence demonstrating up to 85% neuroprotection in the Rose Bengal model (Watson 1998) indicating that there is a salvageable penumbral area. There was a variation in the infarct volumes between the experiments, which was most likely due to the low power of the light source system. Another feature related to the use of regular cold white light is the bell shape of the lesion. This is difficult to overcome except by using laser irradiation beam (Wester et al. 1995, Hu et al. 2001). If laser is available, one can also use the so called photothrombotic ring stroke model, which results in a clear central region-at-risk

(penumbra) surrounded by acutely ischemic territory.

In order to detect true functional deficits and recovery rather than compensatory strategies following brain injury, selection of valid behavioral tests is the key issue. In the present study we used a new modified tapered/ledged beam, which reveals limb impairments in rats long after unilateral ischemic injury. The novel feature of the task is that there are ledges along both sides of the beam, which are 2 cm lower than the upper surface of the beam. This allows assessment of functional outcome relatively independent of practice effects and learned compensation because the ledges provide a crutch on which the animal can place the forelimbs or hindlimbs that slip off the upper beam (Schallert et al. 2002, Schallert and Woodlee 2005). Compensatory adjustment in posture or weight bearing in nonimpaired limbs becomes unnecessary when the animal traverses the beam. Another feature is that the beam is wide at the starting point and tapers gradually to a narrow end near the goal which makes the task more difficult and sensitive.

The match-to-place version of the Morris water-maze test was used, in which the platform is moved to a new location every day. This is a more difficult water-maze version, since the rats have to learn a new location of the platform instead of remembering the previously learned location. No direct comparison of non-probe trial water-maze data between young and aged rats was conducted because some confounding factors such as greater body weight and a possible decline in the visual acuity, motivation, and swimming speed of old rats are known to exist.

Although the functional outcome is remarkably consistent among a variety of unilateral cortical injury models in which sensorimotor regions are damaged, the present results should be confirmed in other experimental stroke models because tissue pathology and reactive neural morphology often differ substantially (Gonzalez and Kolb 2003). Moreover, since in human stroke cases striatal tissue is often severely damaged, these drugs should be examined with an expanded test battery in old animals that have sustained ischemic damage that

extends to rostral aspects of the striatum, which is known to cause more severe and chronic tactile sensory-motor integration deficits and impairments in limb use for reaching, placing, and vertical exploration (Schallert et al. 2000b, Gonzalez and Kolb 2003, Lindner et al. 2003).

6.2. Effect of age on the functional recovery following cortical photothrombosis (II)

The beam-walking test revealed that slip ratio with both forelimbs and hindlimbs was higher in aged rats than in young rats. This may be explained partly by the greater body weight and different strategy used by aged rats. Aged rats not only use digits and pads for locomotion, but also the more distal parts of the heels, which may lead to reduced stimulation of the hindlimb. The similar recovery from impairment in young and aged rats following cortical photothrombosis, however, suggests that there remains plastic capacity to repair and maintain normal function in an aging brain. This result is not consistent with the general view of increased vulnerability of motor functions with age (Schallert 1983, Benecke et al. 1991, Futrell et al. 1991, Carr et al. 1993).

In the water-maze test, despite the more sensitive test design, even aged rats learned the task by the end of the follow-up. The age-related sensorimotor dysfunction may contribute to the impaired water-maze performance in aged rats because the sensorimotor deficit can reduce the amount of information the rats obtain about the location of the hidden platform during spatial learning (Cain 1997). And this deficit can worsen the water maze performance in rats as has been shown in several studies in which prior non-spatial pretraining has eliminated sensorimotor disturbances and impairments in water maze learning (Beiko et al. 1997, Cain 1997, Hoh and Cain 1997). In addition, the present study indicates that a small cortical lesion did not result in water-maze impairment in aged rats which might conceivably be more vulnerable to brain insults.

6.3. Galanthamine and functional recovery in aged rats following cortical photothrombosis (II)

Galanthamine is a selective competitive cholinesterase inhibitor used to treat patients with Alzheimer's disease and vascular dementia (Dal-Bianco et al. 1991, Wilcock et al. 1993, Wilkinson and Murray 2001, Erkinjuntti et al. 2002). Compared with other cholinesterase inhibitors, it has a long plasma half-life, good tolerance, lack of hepatotoxicity, excellent solubility in water and it crosses the blood-brain barrier easily. The possibility that the presence of cholinesterase inhibitors in the brain during and after cerebrovascular events may be beneficial against ischemia-related cell death or recovery process was addressed. When given before an ischemic insult, cholinesterase inhibitors may be protective against ischemic neuronal death (Wu et al. 2000, Zhou et al. 2001, Akasofu et al. 2003) possibly through potentiation of nerve growth factor (Lindefors et al. 1992, Knipper et al. 1994, Lindholm et al. 1994) or by improving cerebral blood flow in areas of moderate ischemia (Sadoshima et al. 1995). After ischemic insults, cholinesterase inhibitors may exert a beneficial effect on sensorimotor and cognitive functions through the same mechanisms (Scremin and Scremin 1986, Scremin et al. 1997, Wang et al. 2002).

In the present study, however, galanthamine did not affect the histological or functional outcome. Nor was it able to reverse age-related spatial learning deficits. This is consistent with the result of a previous study (Barnes et al. 2000). A pure stimulation of the cholinergic system may not be sufficient to achieve a more general age-related spatial learning impairment (Decker and McGaugh 1991, Muller et al. 1994, Cassel and Jeltsch 1995, Steckler and Sahgal 1995, Clayton et al. 2002).

6.4. Acute and long-term effect of risperidone on the functional recovery in aged rats following cortical photothrombosis (I, III)

Elderly patients are often treated with atypical antipsychotics and/or serotonin specific

reuptake inhibiting antidepressants to control mood, aggression and other behavioral problems. Based on previous evidence (Wooltorton 2002), risperidone was anticipated to have a detrimental effect on functional outcome in our aged rats. The present study showed that before cortical infarct, rats treated with risperidone exhibited a slight impairment in beam-walking performance at 2 hours, but not at 24 hours after drug exposure. Subsequently the stroke further exaggerated the deficit at 2 hours, but not at 24 hours. Thus, risperidone, although it did not cause exaggeration of the cortical deficits, the drug had only an acute adverse effect on sensorimotor function that resolves 24 hours after drug exposure. These acute effects are most likely a result of striatal D_2-receptor occupancy leading to impaired extrapyramidal functioning (Tauscher et al. 2002). The sensorimotor impairment by risperidone was similar before cortical photothrombosis and at the end of the follow-up. No significant tolerance had developed despite repeated dosing. In addition, the sensorimotor impairment 24 h after risperidone at the end of the study was similar in ischemic controls and risperidone-treated rats indicating that risperidone does not impair long-term recovery.

The fact that risperidone did not worsen long-term functional recovery in aged rats subjected to cortical stroke is in contrast to the results reported for traditional neuroleptics such as haloperidol (Feeney et al. 1982, Feeney and Westerberg 1990, Goldstein and Bullman 2002). The different neuropathology following cortical ablation and cortical photothrombosis used in the present study may contribute to this difference. Also the different affinity for receptors between haloperidol and risperidone (Arnt and Skarsfeldt 1998) may partially explain their behavioral differences. In addition, some studies have claimed that haloperidol can interfere with mitochondrial electron transport and protein synthesis, generate oxidative metabolites, and decrease choline acetyltransferase enzyme activity (Mahadik et al. 1988, Subramanyam et al. 1991, Prince et al. 1997, Barrientos et al. 1998). These may further contribute to the detrimental effect of haloperidol on recovery whereas no significant effect was observed with risperidone.

We found a significant impairment in water-maze performance 2 hours after risperidone treatment both before and after cortical photothrombosis. Risperidone increased the escape latency and length, the time spent in the outermost annulus, decreased the number of passes over the platform and the time spent in the inner annulus, and decreased swimming speed in agreement with a previous study (Skarsfeldt 1996). The observed impairment was more likely due to factors such as attentional problems, lack of motivation, and particularly motor dysfunction rather than impaired spatial learning. This explanation was strongly supported by results from visible platform task. Aged rats treated with risperidone showed lower performance characterized by decreasing speed and failure to find the visible platform as accurately as sham-operated rats, ischemic controls, or ischemic rats treated with fluoxetine. Only the acute effect of risperidone was studied in the water-maze. However, Terry et al. (2003) showed that long-term (90 days) risperidone exposure did not impair water-maze performance when assessed after a 4 day washout period. However, in this study, risperidone was administered orally in drinking water without assessment of peak plasma concentrations.

The present study showed that risperidone did not affect infarct size following cortical photothrombosis in aged rats. Thus, it is unlikely that risperidone worsens the neuronal damage caused by small strokes, which the elderly probably sustain frequently. This finding is interesting in the light of recent clinical evidence of an increased rate of cerebrovascular events in risperidone-treated dementia patients. It was found that 4% of risperidone-treated dementia patients suffered cerebrovascular adverse events compared with 2% in placebo-treated patients (Wooltorton 2002). A more recent retrospective, population-based cohort study identified 11.400 elderly patients who started treatment with a neuroleptic from 1997 to 2002. The study could not prove statistically significant increase in the risk of stroke in patients receiving either olanzapine or risperidone (Herrmann et al. 2004). The conflicting results between different studies may be due to the inclusion criteria for the cerebrovascular events. Herrmann et al. (2004) did not include cerebrovascular events other than stroke (*e.g.,* transient ischemic attacks, mild strokes), which may have lead to an underestimation of the risks associated with olanzapine and risperidone. Since risperidone did not detectably affect

the ischemic process in aged rats, it might trigger other mechanism(s), including vascular pathology, known to be associated with higher stroke risk in demented patients (Shi et al. 2000).

6.5. Fluoxetine and functional recovery in aged rats following cortical photothrombosis (III)

Our data indicated that fluoxetine treatment was not beneficial or detrimental for sensorimotor recovery in aged rats following focal cerebral ischemia. This is consistent with previous studies (Boyeson et al. 1994, Jolkkonen et al. 2000b, Wilson and Hamm 2002). Fluoxetine is a relatively pure serotonin reuptake blocker and it has little affinity for α-adrenoceptors (Richelson 1984, Stark et al. 1985), which may explain why it has no effect on recovery. Furthermore, it is also possible that acute versus chronic treatments with fluoxetine have different molecular effects. For example, it has been shown that fluoxetine can either increase or decrease levels of CREB, cAMP, brain derived neurotrophic factor and its receptor, tyrosine receptor kinase mRNA depending on whether an acute, short-term, or prolonged dosage schedule is used (Nibuya et al. 1996, Miro et al. 2002, Coppell et al. 2003). This could also explain why a single dose of fluoxetine improved motor function by increasing both speed and strength in behavioural tests and the motor improvement was related to the enhancement of the primary sensorimotor cortex activation (Pariente et al. 2001).

Fluoxetine treatment did not affect the water maze performance of rats before or after cortical photothrombosis. Although serotonergic projections may play a role in age-related spatial learning impairment (Decker and McGaugh 1991, Muller et al. 1994, Cassel and Jeltsch 1995, Steckler and Sahgal 1995, Clayton et al. 2002), the effects of serotonin reuptake inhibitors on water-maze performance have been conflicting (Majlessi and Naghdi 2002, Yau et al. 2002a). Differences in strain, age, and in the level of difficulty among the task, may all contribute to the different results (Lindner and Schallert 1988). Perhaps multiple neurotransmitter systems

are involved and, thus selective manipulation of the serotonergic system by fluoxetine is not in itself sufficient.

The present study also tried to assess the effect of polypharmacy on histological and functional outcome following cortical photothrombosis. In addition to a possible interaction at the level of drug metabolism, the combination of risperidone and fluoxetine is known to produce an additive increase in terms of dopamine and norepinephrine release (Zhang et al. 2000). According to the present data, however, there was no evidence for any significant interaction between risperidone and fluoxetine. The beam-walking performance in the combination group was similar to that obtained with rats given only risperidone 2 and 24 hours after drug administration. The poorer performance by the combination compared with fluoxetine in beam-walking test appeared to be due to the acute effects of risperidone rather than an interaction between the drugs. In the water-maze risperidone and fluoxetine treated rats developed the same kinds of abnormal escape pattern as those treated with risperidone, including increased time in the outermost annulus, decrease in the number of passes over the platform and time spent in the inner annulus, and decreased swimming speed in the hidden or cued platform task. Impaired noncognitive function due to acute effects of risperidone most likely account for this behaviour.

6.6. Zopiclone and functional recovery in aged rats following cortical photothrombosis (IV)

The hypnotic drug, zopiclone, belonging to the chemical class of cyclopyrrolones, is widely prescribed for elderly people. Although structurally unrelated to the benzodiazepines, its pharmacological profile is similar to that of the benzodiazepines. Compared to classical benzodiazepines, however, zopiclone has fewer clinical side effects (*e.g.,* less changes in the EEG patterns of sleep, no rebound effects following drug discontinuation) (Goa and Heel 1986, Musch and Maillard 1990, Wadworth and McTavish 1993). Several experimental studies have demonstrated that GABAergic drugs can alter the recovery of function following brain injury

in rats adversely or beneficially, depending on the site of injury and the timing of the drug treatment (Schallert et al. 1986, Saji and Reis 1987, Schallert et al. 1990, Schallert and Lindner 1990, Shuaib et al. 1992, Shuaib et al. 1993, Hernandez and Holling 1994). Long-term daily treatment with GABAergic drugs such as muscimol, diazepam, or phenobarbital after medial frontal cortex damage has impaired functional recovery and has evoked delayed exaggerated degeneration of remote brain tissue. The present study showed that long-term administration of zopiclone did not worsen the functional outcome, and even slightly improved performance following cortical infarct in our aged rats.

Autoradiographic studies indicate long-term and widespread reduction in $GABA_A$ receptor binding sites in rats subjected to cortical photothrombotic lesions (Schiene et al. 1996, Neumann-Haefelin et al. 1998, Qu et al. 1998a), whereas the number of NMDA receptor binding sites are increased (Que et al. 1999). A downregulation of the α_1-subunit, but not the α_2-subunit, of the $GABA_A$ receptors was noted in an immunohistochemical study (Neumann-Haefelin et al. 1998). The decrease in GABAergic inhibition and the increase in neuronal excitability in the cortical areas adjacent to the ischemic core (Schiene et al. 1996, Hagemann et al. 1998), may contribute to sensorimotor function in rats subjected to cortical photothrombosis. Chronic administration of zopiclone may partially restore altered receptor balance in ischemic rats and in this way modulate the sensorimotor function as found here.

Behavioral deficits can be reinstated by midazolam in stroke patients (Lazar et al. 2002, Lazar et al. 2003) or by diazepam in rats (Schallert et al. 1986, Schallert and Hernandez 1998). Thus, in the present study, rats were administered a single dose of zopiclone after the washout period to assess whether the behavioral deficits would be reinstated. A single dose of zopiclone did not affect the sensorimotor performance. However, ischemic rats previously treated with zopiclone had shorter escape lengths and latencies in the water-maze compared to ischemic controls. It is possible that zopiclone reduced fearfulness or anxiety due to its anxiolytic-like effects (Griebel et al. 1998) in aged rats, which may be sensitive to the stressful test conditions. For example, amitriptyline has been shown to improve water-maze

performance via this kind of mechanism (Miyakawa et al. 1996, Yau et al. 2002b).

Previous studies suggest that GABAergic agents might attenuate neuronal damage following global forebrain ischemia (Shuaib et al. 1993, Schwartz et al. 1994, Schwartz et al. 1995, Shuaib et al. 1995, Schwartz-Bloom et al. 1998). Furthermore, $GABA_A$ receptor agonists reduce infarct volumes after transient (Sydserff et al. 1995, Lyden 1997) and permanent (Sydserff et al. 1995) occlusion of the middle cerebral artery in rats**.** The present study, however, showed that zopiclone did not affect infarct size following cortical photothrombosis in aged rats. GABAergic drugs can also rescue the neurons in the substantia nigra and thalamus, these neurons undergo delayed degeneration following cortical or striatal damage (Saji and Reis 1987, Schallert et al. 1990, Schallert and Lindner 1990, Shuaib et al. 1992, Shuaib et al. 1993). We did not estimate the numbers of neurons in the substantia nigra, but neuronal numbers in thalamic areas were, however, similar in all experimental groups (data not shown) and thus, it is unlikely that thalamic neuroprotection significantly contributed to the observed behavioral improvement.

6.7. Translation to clinical practice

The central nervous system is flexible and plastic and may respond to both external and internal stimuli throughout the lifespan (Bavelier and Neville 2002, Chen et al. 2002). Also the present study demonstrated that the aged brain has a significant plastic capability to repair and maintain normal functioning following focal cerebral ischemia. Thus, advanced age should not be regarded as a limiting factor in the rehabilitation of stroke patients (Paolucci et al. 2003).

After cerebral insults, the aged brain may be fragile and sensitive especially to drug treatment. Retrospective clinical studies in stroke and trauma patients have demonstrated that some older drugs could retard functional outcome, possibly through interfering with brain repair mechanisms (Goldstein 1998, Goldstein 1999, Goldstein 2003). In order to facilitate plastic

changes and to achieve lasting benefits in functional outcome, these detrimental drugs should be avoided. The present work showed that several of the new psychotropic drugs used commonly in the elderly people were relatively safe with respect to possible cerebrovascular events or functional recovery after stroke.

Some of the new drugs such as fluoxetine are known to affect neurotrophic factors and neurogenesis (De Foubert et al. 2004, Kodama et al. 2004, Sairanen et al. 2005), which are important in the functional recovery process. Indeed, fluoxetine improved motor performance in stroke patients (Dam et al. 1996, Pariente et al. 2001). Thus the question must be asked why we could not see any behavioral improvement in the present study? Perhaps the effects taking place at the neuronal level were not reflected at the functional level, or the behavioral tests used may be not sensitive enough to identify positive effects. Alternatively, fluoxetine may act to improve mood and motivation rather than motor performance in stroke patients and thus the positive treatment effects were not seen in animals.

Animal research remains critical to increasing our understanding of the basic mechanisms of injury and recovery, because these experiments can be conducted without ethical restriction such as randomization of treatment and confounding factors such as age, sex, other diseases and medication (Turkstra et al. 2003). The validity and interpretation of recent epidemiological studies about safety of psychotropic drugs are a matter of debate because of the low number of patients examined, and confounded by problems of polypharmacy, compliance, and appropriateness of use (Hartikainen et al. 2003b, Masand and Gupta 2003, Roose 2003, Aparasu and Mort 2004, Baumann et al. 2004, Cohen et al. 2004). Thus, controlled experimental approaches might better address the safety of psychotropic drugs and should be used to support epidemiological and clinical studies.

7. CONCLUSIONS

The present study provides new information concerning the effect of psychotropic medication on functional recovery following cortical stroke in aged rats. The study design was selected to mimic clinical practice in which elderly patients, who have sustained small focal strokes or who are at high risk of stroke, are treated with potent psychotropic medications. The main conclusions are:

1) Galanthamine is not beneficial or harmful with respect to the histological or functional outcome in young or aged rats subjected to cortical photothrombosis (**II**).

2) An atypical neuroleptic, risperidone, does not affect histological or long-term functional outcome in aged rats subjected to cortical photothrombosis whereas the extrapyramidal side effects of risperidone are likely to impair acutely behavioral performance (**I, III**). The selective serotonin reuptake inhibitor, fluoxetine, did not affect histological or behavioral outcome (**III**).

3) Long-term administration of zopiclone, did not worsen functional outcome, and even slightly improved performance following cortical infarct in aged rats (**IV**). After the washout period, a single dose of zopiclone did not affect beam walking performance, but seemed to improve water-maze performance. Infarct size was not affected by zopiclone administration.

Taken together, the present data showed that aged rats can achieve a remarkable functional recovery after cortical stroke. The psychotropic drugs used commonly in the elderly seem to be relatively safe with respect to sensorimotor and cognitive recovery once the treatment was discontinued. Infarct volumes were not affected by the studied drugs.

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