Neurotoxicity Research, 2007, VOL. 12(4). pp. i-iv

F.P. Graham Publishing Co.

Werner J. Schmidt (1950-2007) Pushing the Boundary of Neuroscience: a True Academician and a Complete Gentleman

TREVOR ARCHER[a] and RICHARD J. BENINGER[b]

[a]*University of Göteborg, Department of Psychology, Box 500, SE-45030 Göteborg, and University of Kalmar, HBV, SE-39182 Kalmar, Sweden;* [b]*Departments of Psychology and Psychiatry, Queen's University, Kingston ON K7L 3N6 Canada. trevor.archer@psy.gu.se*

(Submitted 20 August 2007; In final form 01 September 2007)

Prof. Dr. Werner J Schmidt, like Sir Thomas More, was truly 'a man for all seasons'. Character, not temperament, decency, not easy triumphs, integrity, rather than cheap compromise, and respectful love of fellow humankind, not popularity, guided him as he placed family, friends and colleagues, and his science and work at the centre of his life. Throughout our lives we shall never meet a finer human being or friend. Werner was an honest man. He died on April 16, 2007 in Tubingen.

Werner contributed importantly to many areas within the broad field of neuroscience. We will mention a few examples that demonstrate the unique impact that his work has had upon our understanding of brain disease processes. Thus, Werner studied the functional and neurobiological role of *N*-methyl-D-aspartate (NMDA) receptors in different brain regions and their contribution to health and disease. For example, in "Behavioural effects of NMDA-receptor antagonists" published in the *J. Neural Transm.* (Vol. **43**:63-69, 1994), he reviewed the effects of NMDA receptor antagonists in anticonvulsant and anticataleptic activity in a number of behavioural paradigms. In particular he showed that glutamate receptor antagonists produced behavioural effects similar to those of dopamine receptor agonists. In subsequent work with TM Tzschentke he expanded on these basic findings to investigate dopamine-glutamate interactions in reward-related learning (*Neurosci. Lett.* **193**:37-40; 1995; *Behav. Brain Res.* **84**:99-107, 1997) and he combined behavioural and neurochemical testing using intracerebral micordialysis of multiple brain regions to detail the differential mechanisms of action of competitive and non-competitive NMDA receptor antagonists (with W Hauber in *Behav. Brain Res.* **41**:161-166, 1990; with M Bubser, U Keseberg, and PK Notz in *Eur. J. Pharmacol.* **229**:75-82, 1992); these papers collectively produced over 400 citations. Werner integrated his own findings and those of many researchers from European and North American countries in his recent book co-edited with ME Reith, *Dopamine and Glutamate in Psychiatric Disorders* (Humana Press, 2005). This volume contains multiple detailed perspectives on the interactive role of these two neurotransmitter systems in psychiatric diseases, that sets a new standard in understanding the links between brain neuochemical systems and neuropsychiatric disorders. This volume is a good indicator of Werner's major impact on the field of neuroscience.

Werner developed animal models to investigate and understand neurological and psychiatric disease states that afflict humans. For example, in "Low-

*Corresponding author: E-mail: *trevor.archer@psy.gu.se*

ISSN 1029 8428 print/ ISSN 1476-3524 online.

dose challenge by the NMDA receptor antagonist dizocilpine exacerbates the spatial learning deficit in entorhinal-cortex lesioned rats" with U Keseberg, in *Behav. Brain Res.* (Vol. **67**:255-261, 1995) and "Quinolinic acid lesion of the rat entorhinal cortex pars medialis produces selective amnesia in allocentric working memory (WM), but not egocentric WM" with C Holscher in *Behav. Brain Res.* (**63**:187-194, 1994), the neurochemical and functional background of processes leading to dementia were examined. Other animals models pertained to schizophrenia, *e.g.*, "The sigma receptor ligand 1,3-di-(2-tolyl)guanidine in animal models of schizophrenia" with NG Ruckert, in *Eur. J. Pharmacol.* (**233**:261-267, 1993), and "Glycine agonists in the treatment of schizophrenia" with BD Kretschmer, in *Clin. Neuropharmacol.* (**15**:157-161, 1992). In what was to lead to one of Werner's most important discoveries, he developed and/or studied several different animal models of Parkinson's disease, neuroleptic-induced Parkinsonism and Huntington' disease, *e.g.*, in "Excitatory amino acids and Parkinson's disease" with M Bubser and W Hauber, in *Trends Neurosci.* (**13**:46-47, 1990) and "Injection of apomorphine into the medial prefrontal cortex of the rat increases haloperidol-induced catalepsy" with M Bubser, in *Biol. Psychiatry* (**36**:64-67, 1994).

This work gave him much international acclaim, but one area of research endeavour that produced major and outstanding contributions to neuroscience is the techniques and conceptual notions that he developed regarding the intimate glutamate-dopamine interactions underlying Parkinson's disease, schizophrenia and addiction to substances of abuse. For example, in his paper "Dopamine-glutamate interactions in the basal ganglia" in *Amino Acids* (**14**:5-10, 1998), he formulated a working hypothesis of basal ganglia functions involving a process of response selection. Glutamate, being the transmitter of the corticofugal projections to the basal ganglia nuclei and of the subthalamic neurons was thus critically involved in directing the function of dopaminergic systems. Similarly, in "Behavioural pharmacology of glutamate receptors in the basal ganglia" with BD Kretschmer, in *Neurosci. Biobehav. Rev.* (**21**:381-392, 1997), the functional and anatomical outlines of that interaction are delineated. Glutamate-dopamine interactions in substance abuse were outlined in the paper "Glutamatergic mechanism in addiction" with TM Tzschentke, in *Mol. Psychiatry* (**8**:373-382, 2003), which realizes the important role of glutamate in processes underlying the development and maintenance of drug addiction. It is shown that while many actions of glutamate derive from the penchant for a stimulatory interaction with the dopaminergic system, there are some glutamatergic mechanisms that contribute to addiction relatively independently of dopamine. Thus the context-dependent aspects of behaviour depend heavily upon glutamatergic transmission. Particular insights for these interactions in schizopsychotic disorders are provided by "Functional relationship among medial prefrontal cortex, nucleus accumbens, and ventral tegmental areas in locomotion and reward" with TM Tzschentke, in *Crit. Rev. Neurobiol.* (**14**:131-142, 2000), and "Clozapine attenuates the locomotor sensitisation and the prepulse inhibition deficit induced by a repeated oral administration of Catha edulis extract and cathinone in rats" with MY Banjaw and M Fendt, in *Behav. Brain Res.* (**160**:365-373, 2005).

Werner Schmidt made an important impact upon the notion of neuroprotection in brain disorders. For example, in "The neuroprotectant properties of glutamatergic antagonists and antiglutamatergic drugs" with V Pedersen, in *Neurotox. Res.* (**2**:179-204, 2000), they suggested that the complex pattern of neurodegeneration in Parkinson's disease rests on two processes: a 'primary neurodegeneration' occurring in the nigrostriatal dopamine neurons and a 'secondary neurodegeneration' in distant structures of the basal ganglia network. They provided evidence of chronic cellular stress in these structures due to glutamatergic overactivity following initial dopamine loss resulting in 'destructive networks' and they discussed strategies involving reductions in the activities of glutamate pathways as possible therapeutic approaches to neuroprotection.

The sufficient and necessary interactions between noradrenergic and dopaminergic pathways with particular regard to Parkinsonism and other related disorders was another topic explored by Werner and his colleagues. For example, in "Potentiation of parkinsonian symptoms by depletion of locus coeruleus noradrenaline in 6-hydroxydopamine-induced partial degeneration of substantia nigra in rats" with

J Srinivasan, in *Eur. J. Neurosci.* (**17**: 2586-2592, 2003), it was demonstrated that the noradrenaline neurons of the locus coeruleus have neuromodulatory and neuroprotective properties on the dopamine neurons projecting to the basal ganglia and that noradrenergic loss is a contributory factor in the pathophysiology of parkinsonism. Similarly, in "Behavioural and neurochemical effects of noradrenergic depletions with *N*-(2-chloroethyl)-*N*-ethyl-bromobenzylamine in 6-hydroxydopamine-induced rat model of Parkinson's disease" with J Srinivasan, in *Behav. Brain Res.* (**151**: 191-199, 2004), and in "Functional recovery of locus coeruleus noradrenergic neurons after DSP4 lesions: effects on dopamine levels and neuroleptic induced-parkinsonian symptoms in rats" with J Srinivasam, in *J. Neural Transm.* (**111**:13-26, 2004), both the confluence of dopaminergic and noradrenergic pathophysiology and the prerequisites of a functional recovery through noradrenergic hyperinnervation is shown to be the central feature of the neurodegenerative disorder.

Werner discovered a new and exciting phenomenon as part of his most recent work. He found that relatively low doses of dopamine receptor antagonists or submaximal depletions of striatal dopamine that initially had minimal effects on behaviour produced profound behavioural effects upon repeated testing. This effect was specific to the testing environment. He reported these finding in four recent papers: two in *Behav. Pharmacol.* (**14**:563-567, 2003; 14:49-53, 2003; with J Amtage and A Klein, respectively) and one each in *Synapse* (**55**:148-155, 2004; with HB Levsanft, T Kohles and K-A Kovar) and *Behav. Brain Res.* (**156**:181-189, 2005; with MY Banjaw). We had heard Werner present these results at two meetings in the past two years, one in Mazagon, Spain and the other in Krakow, Poland. In both cases his presentations were among the best at the meeting and generated extensive discussion and comment. The implications of these findings are only now beginning to be realized. They suggest that there is a gradual un-learning of the ability to respond to environmental stimuli when repeatedly exposed to those stimuli while activity in the dopamine system is attenuated. This finding has a number of profound implications: It suggests that dopamine normally mediates synaptic changes that enable the ability to respond to regularly encountered environmental stimuli. A reduction in dopamine neurotransmission does not immediately block the ability of an individual to respond to environmental stimuli; rather, it is the combination of this reduction and exposure to the stimuli that leads to the gradual loss. This finding has important implications for understanding the progression of motor symptoms in Parkinson's disease and for understanding responses to medication. For example, these finding might suggest that lower doses of medication will be effective but that their onset of therapeutic action will be delayed and perhaps environment-specific.

Werner's studies of the behavioural and neurochemical effects of dopamine-glutamate interactions achieved international recognition and will continue to do so long into the future. He had just begun a line of work that will lead to one of the most important advances in understanding the progression of symptoms and mechanisms of Parkinson's disease since the work of Nobel laureate Dr. Arvid Carlson showing the important role of dopamine cell loss in Parkinson's and the strong therapeutic response to L-DOPA. Werner would certainly have enjoyed watching this new knowledge unfold.

Werner was on the editorial boards of a number of internationally-renowned scientific journals, he played a major part in the Executive Committee of the *European Behavioural Pharmacology Society*, culminating in his role as President of the Society, and he was plenary speaker at prestigious society meetings, for example the World Congress of Parkinsonism and Related Disorders, the International Meetings of the Neurotoxicity Society and the Strategies in Studying Brain Disorder Meetings. Werner J Schmidt's character was one of outstanding integrity:

"A man who could meet with those two imposters,
Triumph and Disaster, and treat them just the same.
A man who filled the unforgiving minute,
With sixty seconds worth of distance run.
He was a wonderfully great man,
In our sorrow, we are fulfilled by the joy
of having loved him."

[Borrowed from Rudyard Kipling's "*If*"]

Werner as a Welcoming Gentleman

Postscript, added by RM Kostrzewa -

It was during an *Amino Acids* meeting in Chalkadiki, Greece in 1999 when I first met Werner, but it was at another *Amino Acids* meeting, this time in Bonn, Germany in 2001 when I discovered Werner's character. Although I was accompanied by my wife, she was sitting alone while I was engrossed in registering and greeting old and newfound colleagues. Werner found her, introduced himself, and began to talk to her, a non-scientist, and in his quiet but outgoing manner, he continued to converse with her for nearly an hour. It was Werner the Gentleman who displaced Werner the Scientist. It was important to Werner to be welcoming to someone, to anyone, and immediately recognize each as a person of note, including those that had no part in advancing his career. It is this moment, frozen in time, that symbolizes exactly the person that Werner was - a true Gentleman.

References

Amtage J and WJ Schmidt (2003) Context-dependent catalepsy intensification is due to classical conditioning and sensitization. *Behav. Pharmacol.* **14**, 563-567.

Banjaw MY and WJ Schmidt (2005) Behavioural sensitisation following repeated intermittent oral administration of *Catha edulis* in rats. *Behav. Brain Res.* **156**, 181-189.

Banjaw MY, M Fendt and WJ Schmidt (2005) Clozapine attenuates the locomotor sensitisation and the prepulse inhibition deficit induced by a repeated oral administration of *Catha edulis* extract and cathinone in rats. *Behav. Brain Res.* **160**, 365-373.

Bubser M and WJ Schmidt (1994) Injection of apomorphine into the medial prefrontal cortex of the rat increases haloperidol-induced catalepsy. *Biol. Psychiatry* **36**, 64-67.

Bubser M, U Keseberg, PK Notz and WJ Schmidt (1992) Differential behavioural and neurochemical effects of competitive and non-competitive NMDA receptor antagonists in rats. *Eur. J. Pharmacol.* **229**, 75-82.

Hauber W and WJ Schmidt (1990) The NMDA antagonist dizocilpine (MK-801) reverses haloperidol-induced movement initiation deficits. *Behav. Brain Res.* **41**, 161-166.

Holscher C and WJ Schmidt (1994) Quinolinic acid lesion of the rat entorhinal cortex pars medialis produces selective amnesia in allocentric working memory (WM), but not egocentric WM. *Behav. Brain Res.* **63**, 187-194.

Keseberg U and WJ Schmidt(1995) Low-dose challenge by the NMDA receptor antagonist dizocilpine exacerbates the spatial learning deficit in entorhinal cortex-lesioned rats. *Behav. Brain Res.* **67**, 255-261.

Klein A and WJ Schmidt (2003) Catalepsy intensifies context-dependently irrespective of whether it is induced by intermittent or chronic dopamine deficiency. *Behav. Pharmacol.* **14**, 49-53.

Kretschmer BD and WJ Schmidt (1992) Glycine agonists in the treatment of schizophrenia. *Clin. Neuropharmacol.* **15**, 157-161.

Levsanft HB, T Kohles, K-A Kovar and WJ Schmidt (2004) 3,4-Methylenedioxymethamphetamine counteracts akinesia enantioselectively in rat rotational behavior and catalepsy. *Synapse* **55**, 148-155.

Pedersen V and WJ Schmidt (2000) The neuroprotectant properties of glutamatergic antagonists and antiglutamatergic drugs. *Neurotox. Res.* **2**, 179-204.

Reith MEA and WJ Schmidt (2005) *Dopamine and Glutamate in Psychiatric Disorders* (Humana Press:Totowa, NJ).

Ruckert NG and WJ Schmidt (1993) The sigma receptor ligand 1,3-di-(2-tolyl)guanidine in animal models of schizophrenia. *Eur. J. Pharmacol.* **233**, 261-267.

Schmidt WJ (1994) Behavioural effects of NMDA-receptor antagonists. *J. Neural Transm.* Suppl. **43**, 63-69. Review.

Schmidt WJ (1998) Dopamine-glutamate interactions in the basal ganglia. *Amino Acids* **14**, 5-10.

Schmidt WJ and BD Kretschmer (1997) Behavioural pharmacology of glutamate receptors in the basal ganglia. *Neurosci. Biobehav. Rev*. **21**, 381-392.

Schmidt WJ and MEA Reith (2005) Schmidt WJ, M Bubser and W Hauber (1990) Excitatory amino acids and Parkinson's disease. *Trends Neurosci.* **13**, 46-47.

Srinivasan J and WJ Schmidt (2003) Potentiation of parkinsonian symptoms by depletion of locus coeruleus noradrenaline in 6-hydroxydopamine-induced partial degeneration of substantia nigra in rats. *Eur. J. Neurosci.* **17**, 2586-2592

Srinivasan J and WJ Schmidt (2004) Behavioural and neurochemical effects of noradrenergic depletions with *N*-(2-chloroethyl)-*N*-ethyl-bromobenzylamine in 6-hydroxydopamine-induced rat model of Parkinson's disease. *Behav. Brain Res.* **151**, 191-199.

Srinivasan J and WJ Schmidt (2004) Functional recovery of locus coeruleus noradrenergic neurons after DSP4 lesions: effects on dopamine levels and neuroleptic induced-parkinsonian symptoms in rats. *J. Neural Transm.* **111**, 13-26.

Tzschentke TM and WJ Schmidt (1995) *N*-methyl-D-aspartic acid-receptor antagonists block morphine-induced conditioned place preference in rats. *Neurosci. Lett.* **193**, 37-40.

Tzschentke TM and WJ Schmidt (1997) Interactions of MK-801 and GYKI 52466 with morphine and amphetamine in place preference conditioning and behavioural sensitization. *Behav. Brain Res.* **84**, 99-107.

Tzschentke TM and WJ Schmidt (2000) Functional relationship among medial prefrontal cortex, nucleus accumbens, and ventral tegmental areas in locomotion and reward. *Crit. Rev. Neurobiol.* **14**, 131-142.

Tzschentke TM and WJ Schmidt (2003) Glutamatergic mechanism in addiction. *Mol. Psychiatry* **8**, 373-382.