Neural correlates of the anxiolytic effects of Silexan (WS® 1265)

Pia Baldinger[1], Andreas Hahn[1], Christina Rami-Mark[2], Marie Spies[1], Wolfgang Wadsak[2], Anna Höflich[1], Markus Mitterhauser[2], Rupert Lanzenberger[1], Siegfried Kasper[1]

CLINICAL DIVISION OF BIOLOGICAL PSYCHIATRY

[1] Department of Psychiatry and Psychotherapy,
[2] Department of Biomedical and Image-guided Therapy,
Division of Nuclear Medicine
Medical University of Vienna, Austria

MEDICAL UNIVERSITY OF VIENNA

pia.baldinger@meduniwien.ac.at www.meduniwien.ac.at/neuroimaging

INTRODUCTION: Silexan (WS® 1265)[1] is a patented active substance containing an essential oil produced from Lavandula angustifolia flowers and authorized in Germany as a medicinal product for the treatment of restlessness accompanying anxious moods. Its efficacy has been shown in several forms of anxiety disorders. Recently, the superiority of Silexan over placebo and better tolerability compared to paroxetine has been confirmed for generalized anxiety disorder [1]. There is accumulating evidence pointing towards an involvement of the serotonin-1A (5-HT_{1A}) receptor in the pathogenesis and treatment of anxiety disorders [2]. Moreover, anxious phenotypes might be related to morphological brain alterations. Therefore, we aimed at determining the effect of Silexan on serotonin-1A receptor density as well as gray matter volume (GMV) compared to placebo using multimodal brain imaging.

METHODS: A total of 25 healthy men (mean age ± SD = 25.6 ± 3.7) were included in this monocentric, double-blind, randomized, placebo-controlled, cross-over study. Subjects took 2 capsules of the investigational product (each containing 80 mg of Silexan or placebo) per day for at least 8 weeks. The treatment interval was repeated after a wash-out phase of at least 2 weeks. At the end of each treatment period, subjects underwent both positron emission tomography (PET) using the radioligand [*carbonyl*-^{11}C]WAY-100635 and magnetic resonance imaging (MRI, T1-weighted sequence). 19 subjects completed both MRI and 17 subjects both PET measurements. MR data were segmented using the VBM8 toolbox for SPM8 applying the DARTEL algorithm. PET scans were normalized to Montreal Neurological Institute (MNI)-space using SPM8. Quantification of 5-HT_{1A} receptor binding potential (BP_{ND}) was carried out in PMOD 3.3 using SRTM2 and the cerebellar grey as reference region. Repeated-measures analysis of variance (rmANOVA) was computed in SPM8 to compare 5-HT_{1A} BP_{ND} and grey matter volume (GMV, VBM) after Silexan intake versus placebo.

RESULTS: RmANOVA revealed a significant difference in 5-HT_{1A} BP_{ND} following 8 weeks of treatment with Silexan compared to placebo (see figure 1), where 5-HT_{1A} BP_{ND} was found to be reduced in 2 clusters encompassing the left inferior temporal gyrus, left fusiform gyrus, left lingual gyrus, left calcarine gyrus and left hippocampus on one hand (peak t value in the inferior temporal gyrus: t=-6.64, k=5334, p<0.05, FWE corrected at cluster-level, x/y/z=-38/-52/-6mm MNI space), and the right insula, right putamen, right anterior cingulum, right caudate, right medial superior frontal gyrus and right inferior orbitofrontal gyrus on other hand (peak t value in the right insula: t=-6.08, k=4812, p<0.05, FWE corrected at cluster-level, x/y/z=34/0/20mm MNI space). Results are summarized in the table. Regarding grey matter volume (VBM analysis), the rmANOVA revealed no results withstanding FWE-correction.

[1]Silexan is the active substance of Lasea®, manufacturer: Dr. Willmar Schwabe GmbH & Co. KG

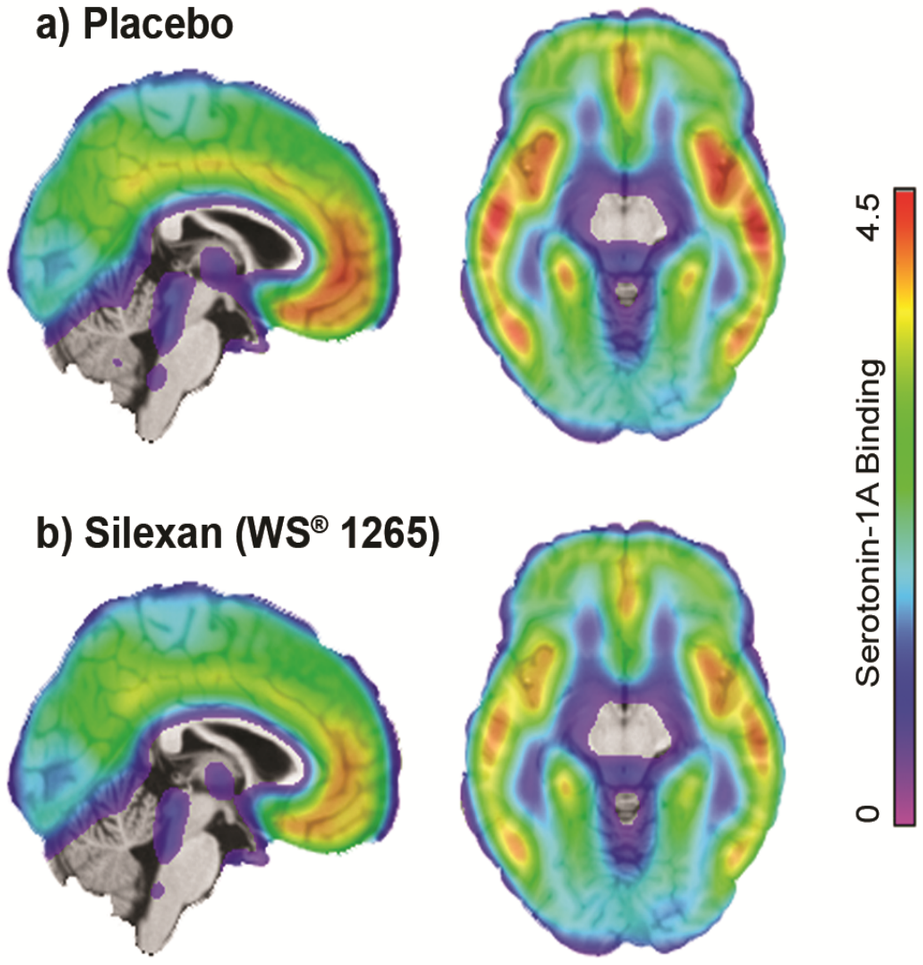

Figure 1. Average serotonin-1A receptor binding potential (BP_{ND}) of 17 healthy men after chronic administration of (**a**) placebo or (**b**) Silexan. PET data are superimposed on a sagittal and axial view of a structural magnetic resonance imaging template. The color table indicates the 5-HT_{1A} receptor binding potential. A reduced 5-HT_{1A} receptor binding after the intake of Silexan can be observed in several brain regions.

Anatomical Region (AAL)	MNI coordinates			Statistics		
	x	y	z	T	Cluster size	% difference
Inferior temporal gyrus_L	-38	-52	-6	-6.64	5334*	-15.5±10.4
Fusiform gyrus_L	-30	-57	-6	-6.42	5334*	-16.8±11.2
Insula_R	34	0	20	-6.08	4812*	-18.1±13.6
Lingual gyrus_L	-12	-42	2	-5.48	5334*	-14.1±11.0
Precuneus_R	9	-52	16	-5.16	1881	-12.7±11.3
Middle cingulum_L	-10	-27	51	-4.69	1211	-15.1±12.3
Lingual gyrus_R	14	-90	-8	-4.51	933	-11.8±12.1
Calcarine gyrus_L	-26	-57	8	-4.33	5334*	-16.8±18.9
Hippocampus_L	-26	-28	-8	-4.26	5334*	-14.4±16.3
Putamen_L	-24	6	-6	-4.17	449	-12.6±12.4
Cerebellum_R	12	-66	-50	-4.02	368	-32.7±39.1
Putamen_R	24	-6	8	-5.23	4812*	-30.2±24.4
Anterior cingulum_R	4	45	-4	-3.88	4812*	-9.8±11.9
Middle temporal gyrus_L	-66	-24	-8	-3.71	445	-12.4±14.9
Medial superior frontal gyrus_R	8	56	2	-3.44	4812*	-9.9±13.3
Middle temporal gyrus_R	50	-4	-18	-3.43	605	-7.7±12.3
Precuneus_L	-9	-64	26	-3.16	5334*	-9.3±14.2
Caudate_R	8	21	9	-3.14	4812*	-9.9±43.5
Inferior orbitofrontal gyrus_R	20	27	-20	-2.97	4812*	-9.5±15.3

Table. Regional peak t-values are shown following repeated-measures ANOVA comparing 5-HT_{1A} receptor binding potential after prolonged intake of Silexan compared to placebo. T-values are given for comparisons with p<0.005 uncorrected for multiple comparisons, voxel-level; *p<0.05 FWE corrected, cluster-level. Only clusters with >284 voxels are shown as given by SPM8's expected voxels per cluster. Same cluster size indicates that regions are interconnected within one cluster. Percentage difference (mean±sd) in 5-HT_{1A} binding is computed as ($BP_{ND\_Silexan}$ – $BP_{ND\_Placebo}$) / $BP_{ND\_Placebo}$ * 100. Abbreviations: AAL Automated Anatomical Labeling, MNI Montreal Neurologic Institute, R right, L left

CONCLUSIONS: We detected a widespread reduction of serotonin-1A receptor density after prolonged Silexan intake compared to placebo. This is in line with previous findings showing a reduction of 5-HT_{1A} BP_{ND} following chronic treatment of patients with anxiety disorders [3]. The anxiolytic effect of Silexan might therefore be reflected within variations of the serotonin-1A receptor, which is one of the major players in the neurobiology of anxiety. Silexan did not induce changes on a structural level; its effects might predominantly be associated with changes in receptor expression and affinity.

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[1]Medical University of Vienna, Dept of Psychiatry and Psychotherapy, Vienna, Austria

[2]Medical University of Vienna, Dept of Biomedical Imaging and Image-guided Therapy Division of Nuclear Medicine, Vienna, Austria

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Results: RmANOVA revealed a significant difference in 5-HT_{1A} BP_{ND} following 8 weeks of treatment with Silexan compared to placebo, where 5-HT_{1A} BP_{ND} was found to be reduced in 2 clusters encompassing the left inferior temporal gyrus, left fusiform gyrus, left lingual gyrus, left calcarine gyrus and left hippocampus on one hand (peak t value in the inferior temporal gyrus: t=−6.64, k=5334, p<0.05, FWE corrected at cluster-level, x/y/z=−38/-52/-6mm MNI space), and the right insula, right putamen, right anterior cingulum, right caudate, right medial superior frontal gyrus and right inferior orbitofrontal gyrus and on other hand (peak t value in the right insula: t=−6.08, k=4812, p<0.05, FWE corrected at cluster-level, x/y/z=34/0/20mm MNI space). Regarding GMV, rmANOVA revealed no results withstanding FWE-correction.

Conclusions: We detected a widespread reduction of serotonin-1A receptor density after prolonged Silexan intake compared to placebo. This is in line with previous findings showing a reduction of 5-HT_{1A} BP_{ND} following chronic treatment of patients with anxiety disorders [3]. The anxiolytic effect of Silexan might therefore be reflected within variations of the serotonin-1A receptor, which is one of the major players in the neurobiology of anxiety. Silexan did not induce changes on a structural level; its effects might predominantly be associated with changes in receptor expression and affinity.

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Keywords

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