社会的治療がより重要視されるようになってきている。このような流れの中で，QOLの向上を目指した治療が重要視されるようになってきたといえる。

統合失調症患者のQOL評価では，客観的評価尺度であるQuality of Life Scale (QLS)[8]の使用頻度が高く，一定の評価を得ているように思われる。QLSは非入院の統合失調症患者のQOLを半構造化面接に基づいて評価するものであり，統合失調症の欠損症状とそれにより派生してくる対人関係面の障害，社会的機能の障害を総合的に評価する尺度として開発されたものである。QLSは「対人関係と社会的ネットワーク」，「仕事・学校・家事などの役割遂行」，「精神内界の基礎」，「一般的所持品と活動」の4つのサブスケールからなる21項目を0～6点の範囲でスコア化し評価するように作成されている。従来は，このような医療スタッフによるQOL評価が行われることが多かったが，World Health Organization (WHO)によると，QOLとは身体的側面・心理的側面・自立レベル・他者との関係・環境・精神性/宗教/信念の領域に対する個人の主観的認知により決定されるもの，と定義されていることから，本人の主観的評価が基本的に重要である。このような観点から，統合失調症患者においても主観的QOL評価の必要性が議論され，それは必然的に患者の主観的評価に信頼性があるのかどうかという論争を呼び起こした。しかし，これまでの研究結果から，近年では急性期以外で精神症状がある程度安定している患者の自己評価については十分な信頼性があるという見解が大勢を占めるようになっている[29]。

主観的QOL評価尺度としては，わが国では一般的QOL評価尺度であるWHO QOL-26や健康関連QOL評価尺度であるMedical Outcome Study Short Form-36 (SF-36)などがよく用いられているが，これらは統合失調症患者での使用を想定して作られていない。欧米では，統合失調症患者を対象とした疾患特異的な主観的QOL評価尺度がいくつか開発されているが，その中の1つに，Wilkinsonら[29]が開発したSchizophrenia Quality of Life Scale (SQLS)がある。SQLS日本語版の信頼性・妥当性はすでに検証されて報告されており[10]，わが国でも臨床や研究で用いられる頻度が増えてきている。SQLSは統合失調症患者の認知と関心を測定する自己記入式質問表であり，「心理社会関係」，「動機と活力」，「症状と副作用」の3つの領域にわたる30項目で構成されている。各項目を0～4点で自己採点し，各領域のスケールスコアを算出するものであり，スコアが低いほど主観的QOLが良好なことを示している。その他の統合失調症に特異的な尺度としては，QOLの重要な構成要素である主観的ウェルビーングを測定する評価尺度として，Naberら[17]の開発したSubjective Well-being under Neuroleptic drug treatment Short form (SWNS)があり，日本語版の信頼性と妥当性もすでに検証されている[28]。SWNSは20項目からなり，「精神機能」，「セルフコントロール」，「感情調節」，「身体機能」，「社会的統合」の5つのサブスケールを持っている。

主観的QOL評価は，評価者による客観的QOL評価との関係が常に問題となる。現実的な問題として，たとえば，無為・自閉的で他者とかかわりを持たず，ひきこもっているような患者や現実検討ができず誇大的思考を持つ患者では客観的QOLは低くなるが，患者自身はQOLを肯定的に認識しているということが十分あり得る。このようなケースの存在を考慮すると，やはり，ある程度の精神症状を持つ患者では，主観的QOL評価のみでQOLを評価することには無理があると思われる[23]。これまでも主観的QOLと客観的QOLの間に乖離が存在するとの報告が散見されたため，我々は，外来通院中の精神症状の安定した統合失調症患者99名を対象にSQLSとQLSを用いて患者のQOLを評価し，両者の関係を検討した[22]。その結果，SQLSの「動機と活力」スコアはQLS総スコアとそのサブスケールである「対人関係と社会的ネットワーク」スコア，「仕事・学校・家事などの役割遂行」スコア，「精神

内界の基礎」スコア，「一般的所持品と活動」スコアとそれぞれ有意な相関を示し，SQLSの「心理社会関係」スコアはQLS総スコアと有意な相関を示したが，これらはいずれもきわめて弱い相関であった。一方，SQLSの「症状と副作用」スコアはQLSとは有意な相関を示さなかった。さらに，罹病期間や1日当たりの抗精神病薬服用量，入院回数，陽性症状，陰性症状，抑うつ症状，薬原性錐体外路症状を説明変数とし，SQLSおよびQLSを目的変数とした重回帰分析の結果から，SQLSスコアとQLSスコアに最も影響を及ぼしているのは，それぞれ抑うつ症状と陰性症状であることが明らかになった。これらの結果は，統合失調患者の主観的QOLと客観的QOLとの間にはやはり乖離があり，両者の主な予測因子が異なることを示している。

以上のことから，統合失調症患者のQOLを評価する際には，主観的QOLと客観的QOLの違いに注意しておく必要があり，さらに，臨床や研究でQOLを測定する場合は，どちらか一方のQOL評価法を採用するのではなく，両者を相互補完的に用いて評価すべきであると我々は考えている[22,23]。

生活技能と社会機能

近年，統合失調症患者の地域社会での自立や社会復帰に向けたリハビリテーションの重要性が高まっており，同時にその効果を適切に評価することが必要となってきている。リハビリテーションの主な対象となるのは地域で生活している患者になるが，そのような患者を対象とした生活技能についての実用性のある評価尺度はそれほど多くない。Rosenら[18]によって開発されたLife Skills Profile(LSP)は，主として地域の居住施設で暮らしている統合失調症患者を対象として，その機能と障害を測定するための評価尺度であり，地域での生活適応に関する機能に焦点が当てられている。LSPは非専門家でも使えるように平易な内容になっており，評価に際して特別な訓練を要しない。LSPは39項目からなり，それぞれの項目は，過去3か月の対象者の全般的な生活行動に基づいて，正常な機能(4点)から最も重い障害(1点)までの4段階で評価され，「身辺整理」，「規則順守」，「交際」，「会話」，「責任」の5つのサブスケールを有している。LSP日本語版の信頼性と妥当性についてはすでに報告されている[7]。

LSP以外で統合失調症患者の社会生活全般にわたる障害を評価できるものとしては，わが国で開発されたLife Assessment Scale for the Mentally Ill(LASMI)[9]が挙げられる。LASMIは豎[27]のいう統合失調症者の「生活のしづらさ」を参考にして構成されており，「日常生活」，「対人関係」，「労働または課題の遂行」，「持続性・安定性」，「自己認識」の5つの領域について評価するものである。LASMIも採点にあたって特別な訓練を要せず，患者の生活をよく知るものであれば妥当な評価ができるようになっているため，作業所やデイケアなどで患者と日中の生活を共にしている医療スタッフが評価することが可能であり，実用的なスケールといえる。それ以外では，主として入院中の患者を対象とした尺度として，地域での生活可能性のアセスメントおよび支援の効果判定のために用いられるRehabilitation Evaluation of Hall and Baker(REHAB)[3]が挙げられる。日本語版も用意されており[4]，わが国でも使用頻度が増えてきている。REHABは合計23項目からなり，「逸脱行動」，「社会的活動」，「言葉のわかりにくさ」，「セルフケア」，「社会生活の技能」の領域が評価できる。なお，REHABの評価は専門家によって行われることになっている。また，患者の全般的機能レベルの評価尺度としてよく知られた簡便なものにGlobal Assessment of Functioning(GAF)[2]がある。GAFは精神的健康と病気という1つの仮想的な連続体に沿って心理的，社会的，職業的機能の側面から患者の機能を全体的に評価する尺度であり，100点を満点としてスコアが高いほど健康度が高いことを示している。しかし，GAFについては，社会機能の評価が精神症状と結びつけて記述されていることに対する批判があり，患者の全般的機能を

表1 Life Skills Profile (LSP) と Schizophrenia Quality of Life Scale (SQLS) および Quality of Life Scale (QLS) の相関 (文献1) の Table 2 を一部改変)

	SQLS			QLS				
	心理社会関係	動機と活力	症状と副作用	総スコア	対人関係と社会的ネットワーク	仕事・学校・家事などの役割遂行	精神内界の基礎	一般的所持品と活動
LSP								
総スコア	−0.47**	−0.41*	−0.46**	0.55**	0.48**	0.56**	0.49**	0.47**
身辺整理	−0.40*	−0.32	−0.43**	0.52**	0.46**	0.54**	0.45**	0.49**
規則順守	−0.44**	−0.25	−0.43**	0.16	0.08	0.24	0.17	0.13
交際	−0.36	−0.44**	−0.28	0.63**	0.57**	0.57**	0.57**	0.50**
会話	−0.33	−0.31	−0.37*	0.37	0.32	0.39*	0.33	0.27
責任	−0.24	−0.17	−0.25	0.26	0.22	0.29	0.23	0.26

*$p<0.05$, **$p<0.01$ (Bonferroni 補正)

評価するにはGAF単独では不十分であるとされている[19]。

我々は以前に，64名の精神症状の安定した統合失調症外来患者を対象に生活技能のレベルとQOLの関係を検討した[1]。前述のSQLSとQLSを用いて主観的QOLと客観的QOLを測定し，患者と同居している家族にLSPの評価を依頼した。その結果，LSP総スコアは，SQLSの「心理社会関係」，「動機と活力」，「症状と副作用」の各スケールと有意な相関を認め，QLSの総スコアと4つのサブスケールすべてと有意な相関が認められ，生活技能レベルが高いほど主観的QOLと客観的QOLの両方が良好であることが確認された (表1)。さらに，生活技能レベルと関連する臨床要因を明らかにするために，LSP総スコアを目的変数，陽性症状スコア，陰性症状スコア，抑うつ症状スコア，薬原性錐体外路症状スコアなどの臨床指標を説明変数として重回帰分析を行った結果，LSPに最も影響を与えている因子は，陰性症状と抑うつ症状であることが示された。

認知機能

統合失調症では，幻覚・妄想といった陽性症状や感情鈍麻，自閉，活動性低下といった陰性症状以外にも抑うつ症状や認知機能障害が認められる[21]。そして，これらの症状や障害は，リハビリテーションにおけるスキルの獲得，コミュニティへの適応，仕事での能力の発揮といった機能的アウトカムにおける障害へとつながる。特に，近年，統合失調症患者の認知機能障害は就労などの社会的予後と関係した重要な障害として注目されるようになっている。統合失調症患者の就労の問題は費用的にも重要である。疾病にかかわる費用には直接費用と間接費用があるが，統合失調症にかかわる間接費用については，低い就労率や労働能力の低下が大きく影響している。これまでも，統合失調症の就労率は先進国においては15%以下であったとの報告[16]があるが，現在も依然として低い就労率にとどまったままである。その背景に認知機能障害があると考えられることから，近年では，認知機能障害の改善を目指す治療が注目されている。

薬物療法の視点から認知機能障害をみた場合，否定的な報告もあるが，全体的にみて，非定型抗精神病薬による治療が認知機能障害を有意に改善させたとする報告が多い。Keefeら[14]は15の研究のメタ解析を行い，注意，遂行機能，ワーキングメモリー，言語流暢性などに関して，定型抗精神病薬よりも非定型抗精神病薬のほうが有意に改善効果があったと報告している。HarveyとKeefe[6]も20の研究報告のメタ解析を行い，非定型抗精神病薬には認知機能全般を改善させる効果があると報告している。しかし，これまでの研究は，ほとんどが高用量の定型抗精神病薬と適量の

表2　Brief Assessment of Cognition in Schizophrenia (BACS) と Quality of Life Scale (QLS) の相関 (文献26) の Table 2 を一部改変)

	QLS				
	総スコア	対人関係と社会的ネットワーク	仕事・学校・家事などの役割推古	精神内界の基礎	一般的所持品と活動
BACS					
言語性記憶	0.419**	0.415**	0.311	0.422**	0.295
ワーキングメモリー	0.281	0.283	0.142	0.290	0.259
運動機能	0.196	0.175	0.126	0.222	0.228
注意と情報処理スピード	0.515**	0.495**	0.372*	0.541**	0.418**
言語流暢性	0.203	0.200	0.154	0.206	0.170
遂行機能	0.168	0.174	0.103	0.131	0.175
コンポジット・スコア	0.341*	0.346*	0.205	0.341*	0.305

*$p<0.05$, **$p<0.01$ (Bonferroni 補正)

非定型抗精神病薬の比較であり，明らかに後者に有利なデザインとなっている。最近の米国の大規模試験では，適量に設定された定型抗精神病薬のペルフェナジンが認知機能改善において新規非定型抗精神病薬より優越する傾向を示すという結果となっている[12]。また，認知機能リハビリテーションによっても認知機能障害を改善できることが報告されており[15]，認知機能の改善をアウトカム指標の1つに加える必要性が高まってきている。

これまで統合失調症患者の認知機能の評価には，各領域を評価するいくつかの検査を目的に応じて組み合わせた神経心理学的テストバッテリーが用いられてきたが，バッテリーの内容はさまざまであり，研究者や施設間でのばらつきが大きいため，検査結果の比較が困難であった。近年，統合失調症患者の認知機能を，包括的かつ簡便に測定し得るテストバッテリーとして，Keefe ら[13]によって Brief Assessment of Cognition in Schizophrenia (BACS) が開発された。BACS は「言語性記憶」，「ワーキングメモリー」，「運動機能」，「注意と情報処理スピード」，「言語流暢性」，「遂行機能」の6つの領域を評価でき，検査に要する時間も30〜40分程度と短いため，臨床現場で使用しやすい。BACS 日本語版の信頼性・妥当性についてはすでに検討されている[11]。

我々は，61名の精神症状の安定している外来通院中の統合失調症患者を対象に認知機能と客観的 QOL の関係を検討した[26]。その結果，BACS composite スコアは QLS 総スコアと有意な正の相関が認められた。BACS の各領域では，「注意と情報処理スピード」と「言語性記憶」は QLS 総スコアと有意な正の相関が認められた (表2)。また，精神症状などを説明変数に入れた重回帰分析の結果からは，QLS 総スコアに独立して影響を与える要因としては，陰性症状と抑うつ症状が重要であったが，BACS の「注意と情報処理スピード」も QLS に独立して影響を与えていることが明らかとなった。我々はまた，主観的 QOL と認知機能の関係についても検討しており，両者にはほとんど有意な相関が認められないことを報告している[25]。

さらに最近では，米国国立精神保健研究所 (NIMH) 主導のもと，米国食品医薬品局 (FDA)，学界，製薬企業が連携して，「統合失調症における認知機能の改善のための測定と治療研究 Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)」と呼ばれるプロジェクトが企画され，統合失調症患者の認知機能を改善する薬物の治験に使用可能な認知機能評価バッテリー (MATRICS consensus cognition battery；MCCB) を開発した。MCCB は，「処理速度」，「注意/覚醒」，「ワーキングメモリ

ー」,「言語学習」,「視覚学習」,「推論と問題解決」,「社会認知」の7つの認知機能領域を評価し,信頼性・妥当性もすでに検証されている。現在,わが国でもMCCB日本語版の標準化作業が進行中である[20]。

一方で,認知機能の評価においては,検査を繰り返し施行することによって,予想以上に練習効果が試験成績に影響することが指摘されている[5]。このため,薬物療法や認知機能リハビリテーションの認知機能改善効果の評価に際しては,コントロールを置いて練習効果の影響を検討したうえで改善効果を評価するといった,より洗練された研究デザインを組む必要があるだろう。

おわりに

以上,統合失調症治療におけるアウトカム指標について概説した。最初に述べたように治療がリハビリテーションの段階に移ると,生活技能や社会機能,QOLの評価がより重要となるが,これらに影響を与える要因として,陰性症状や抑うつ症状が重要であることがわかっているため,治療においてもそれらを改善したり,最小限にとどめる工夫が大切である。

また,近年注目されている認知機能障害については,Neuropsychological Education Approach to Rehabilitation (NEAR)などの直接的に認知機能障害の改善を目指す認知機能リハビリテーションが注目されてきているが,認知機能障害の改善の評価は,より生活に密着した指標である生活技能や社会機能,QOLの評価と合わせて行われるべきものであると我々は考えている。

文献

1) Aki H, Tomotake M, Kaneda Y, et al : Subjective and objective quality of life, levels of life skills, and their clinical determinants in outpatients with schizophrenia. Psychiatry Res 158 : 19-25, 2008
2) American Psychiatric Association : Diagnostic and Statistical Manual of Mental Disorders, 4th ed, APA, Washington DC, 1994
3) Baker R, Hall JN : REHAB A new assessment instrument for chronic psychiatric patients. Schizophr Bull 14 : 97-111, 1988
4) 藤信子,田原明夫,山下俊幸:デイケアとその評価.精神科診断学 5 : 162-172, 1994
5) Goldberg TE, Goldman RS, Burdick KE, et al : Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia : Is it a practice effect? Arch Gen Psychiatry 64 : 1115-1122, 2007
6) Harvey RD, Keefe RS : Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 158 : 176-184, 2001
7) 長谷川寮一,小川一夫,近藤智恵子,他:Life Skills Profile (LSP)日本語版の作成とその信頼性・妥当性の検討.精神医学 39 : 547-555, 1997
8) Heinrichs DW, Hanlon TE, Carpenter WT : The Quality of Life Scale : An instrument for rating the schizophrenic deficit symptoms. Schizophr Bull 10 : 388-398, 1984
9) 岩崎晋也,宮内勝,大島巌,他:精神障害者社会生活評価尺度の開発—信頼性の検討.精神医学 36 : 1139-1151, 1994
10) Kaneda Y, Imakura A, Fujii A, et al : Schizophrenia quality of life scale : Validation of the Japanese version. Psychiatry Res 113 : 107-113, 2002
11) Kaneda Y, Sumiyoshi T, Keefe R, et al : Brief assessment of cognition in schizophrenia : Validation of the Japanese version. Psychiatry Clin Neurosci 61 : 602-609, 2007
12) Keefe RS, Bilder RM, Davis SM, et al : Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry 64 : 633-647, 2007
13) Keefe RS, Goldberg TE, Harvey PD, et al : The Brief Assessment of Cognition in Schizophrenia : Reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 68 : 283-297, 2004
14) Keefe RS, Silva SG, Perkins DO, et al : The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia : A review and meta-analysis. Schizophr Bull 25 : 201-222, 1999
15) McGurk SR, Twamley EW, Sitzer DI, et al : A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry 164 : 1791-1802, 2007

16) Mulkern VM, Manderscheid RW：Characteristics of community support program clients in 1980 and 1984. Hosp Community Psychiatry 40：165-172, 1989
17) Naber D, Moritz S, Lambert M, et al：Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res 50：79-88, 2001
18) Rosen A, Hadzi-Pavlovic D, Parker G, et al：The Life Skills Profile：A measure assessing function and disability in schizophrenia. Schizophr Bull 15：325-337, 1989
19) Roy-Byrne P, Dagadakis C, Unutzer J, et al：Evidence for limited validity of the revised global assessment of functioning scale. Psychiatr Searv 47：864-866, 1996
20) 佐藤拓，兼田康宏，住吉チカ，他：MATRICSコンセンサス認知機能評価バッテリーの開発―統合失調症治療への導入を目指して．臨精薬理 13：289-296, 2010
21) Taniguchi T, Sumitani S, Aono M, et al：Effect of antipsychotic replacement with quetiapine on the symptoms and quality of life of schizophrenic patients with extrapyramidal symptoms. Hum Psychopharmacol 21：439-445, 2006
22) Tomotake M, Kaneda Y, Iga J, et al：Subjective and objective measures of quality of life have different predictors in people with schizophrenia. Psychol Rep 99：477-487, 2006
23) 友竹正人，兼田康宏，大森哲郎：主観的QOLの観点からみた統合失調症の合理的な薬物療法．精神科 4：171-175, 2004
24) 友竹正人，大森哲郎：統合失調症と抑うつ―症候論と薬物療法について．臨精薬理 6：1419-1426, 2003
25) Tomotake M, Ueoka Y, Tanaka T, et al：Effect of cognitive dysfunction on subjective quality of life in people with schizophrenia. British Association of Behavioural and Cognitive Psychotherapies-38th Annual Conference, Manchester, 2010
26) Ueoka Y, Tomotake M, Tanaka T, et al：Quality of Life and cognitive function in people with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry (in press)
27) 蜜　弘：リハビリテーションプログラムとその効果，精神疾患．医学のあゆみ 116：538-544, 1981
28) 渡辺美智代，松村人志：抗精神病薬治療下主観的ウェルビィーング評価尺度短縮版の日本語版作成とその信頼性と妥当性の検討．臨精薬理 6：905-912, 2003
29) Wilkinson G, Hesdon B, Wild D, et al：Self-report quality of life measure for people with schizophrenia：The SQLS. Br J Psychiatry 177：42-46, 2000
30) Yamauchi K, Aki H, Tomotake M, et al：Predictors of subjective and objective quality of life in outpatients with schizophrenia. Psychiatry Clin Neurosci 62：404-411, 2008

Adv Ther (2010) 27(5): .
DOI 10.1007/s12325-010-0035-4

ORIGINAL RESEARCH

Serotonin-1A Receptor Gene Polymorphism and the Ability of Antipsychotic Drugs to Improve Attention in Schizophrenia

Tomiki Sumiyoshi · Masahiko Tsunoda · Yuko Higuchi · Toru Itoh · Tomonori Seo · Hiroko Itoh · Michio Suzuki · Masayoshi Kurachi

Received: April 20, 2010 / Published online:

ABSTRACT

Introduction: The purpose of this study was to determine if the functional single nucleotide polymorphisms of rs6259 C(-1019)G in the promoter region, which regulates serotonin 5-HT_{1A} receptor transcription, affects the ability of antipsychotic drugs to improve attention in patients with schizophrenia. ***Methods:*** Subjects were neuroleptic-free and meeting DSM-IV-TR criteria for schizophrenia. Psychopathology and attention were evaluated with the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) at baseline and 3 months after treatment with atypical antipsychotic drugs (AAPDs). DNA was extracted from peripheral blood following standard procedures. Genotyping was performed with HS-Taq assay (LaboPass™). ***Results:*** Data were available from 30 subjects (male/female=19/11), in which 17 had the CC genotype, three had the GG genotype, and 10 were heterozygous. The 3-month treatment with AAPDs was associated with significant improvements in positive and negative symptoms, but not attention as measured by SANS-Attention subscale in the entire subject group. There were no significant differences in the degree of improvements of SAPS and SANS scores between the CC genotype group and the (C/G plus G/G) combined group. On the other hand, improvement of attention was significantly greater for the former group compared to the latter group ($P<0.016$), suggesting a detrimental influence of the G-allele. ***Conclusions:*** These results provide additional support to the role of 5-HT_{1A} receptors in some of the cognitive disturbances of schizophrenia. Further studies with a larger number of subjects are warranted.

Tomiki Sumiyoshi (✉) · Masahiko Tsunoda · Yuko Higuchi · Toru Itoh · Tomonori Seo · Hiroko Itoh · Michio Suzuki · Masayoshi Kurachi
Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, 2630 Sugitani, Toyama 930-0194, Japan.
Email: tomikisumiyoshi840@hotmail.com

Tomiki Sumiyoshi · Michio Suzuki · Masayoshi Kurachi
Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation, Tokyo, Japan

Keywords: atypical antipsychotic drugs; cognition; pharmacogenetics; schizophrenia; SNPs; 5-HT_{1A}

INTRODUCTION

Disturbances of cognitive function, such as verbal memory, attention, executive function, and verbal fluency, have been reported to determine outcome in patients with schizophrenia.[1,2] Among the domains of cognition, attention/vigilance has been widely studied as a measure of impaired frontal lobe function, which is characteristic of schizophrenia.[1-3] Therefore, efforts to address specific domains of cognition, such as attention, are needed in the treatment of schizophrenia.

A growing number of investigations have been directed to several types of serotonin (5-HT) receptors, such as 5-HT_{1A} and 5-HT_{2A} receptors, in the pathophysiology and treatment of schizophrenia.[4-9] Postmortem[10,11] and positron emission tomography[12,13] studies report altered expression of 5-HT_{1A} receptors in frontal and temporal cortical regions in patients with schizophrenia and related psychoses, while others[14] do not. Accordingly, ipsapirone (a 5-HT_{1A} partial agonist)-induced plasma cortisol response has been found to be blunted in female patients with schizophrenia.[15] These findings are consistent with the concept that 5-HT_{1A} receptors play an important role in the cognitive disturbances of schizophrenia.[6,16,17]

Based on these lines of evidence, we previously conducted a series of studies on the effects of the addition of 5-HT_{1A} partial agonists (eg, buspirone[3] and tandospirone[18,19]) to ongoing treatment with typical or atypical antipsychotic drugs on cognitive function in patients with schizophrenia. In a randomly assigned, placebo-controlled, double-blind study, augmentation therapy with buspirone was found to selectively improve cognitive performance on the digit symbol substitution test, a measure of attention/speeded motor performance, but not other domains of cognition, in subjects with schizophrenia treated with atypical antipsychotic drugs (AAPDs).[3] However, positive and negative psychotic symptoms were not significantly affected.[3] As genetic variations have been suggested to affect cognitive performance, pharmacogenetic approaches may provide further insights into treatment development.[20]

Polymorphisms of genes encoding specific 5-HT receptor subtypes, such as 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}, have been suggested to predict response to treatment with antipsychotic drugs.[21-25] Among these polymorphisms, functional single nucleotide polymorphisms (SNPs) of 5-HT_{1A} receptors, eg, rs6295 C(-1019)G in the promotor region of the 5-HT_{1A} receptor, have been a focus of extensive research on psychiatric diseases.[7,9,22,25-27] C(-1019)G regulates 5-HT_{1A} receptor transcription, and subjects with G-allele homozygotes show elevated 5-HT_{1A} receptor density in presynaptic raphe neurons, which is associated with major depression and anxiety. On the other hand, C-allele carriers elicit a better response to treatment with AAPDs[22,25] or antidepressants,[28-31] although controversy exists.[32]

Intrinsic 5-HT_{1A} agonist activity of the AAPDs, by causing an increase in dopamine (DA) and/or acetylcholine release, has been suggested to provide a basis for the ability of these compounds to improve specific domains of cognition,[33,34] such as attention.[7] In support of this view, the 5-HT_{1A} antagonist WAY 100635 inhibits the increase in DA release produced by AAPDs, such as clozapine and ziprasidone, which are themselves 5-HT_{1A} partial agonists,[33,35] as well as olanzapine and risperidone, which do not directly interact with 5-HT_{1A} receptors.[33,36] These observations indicate that the ability of AAPDs to enhance cognition is dependent on the 5-HT_{1A} receptor function, irrespective of type of compounds.

In view of accumulated evidence, discussed above, it was hypothesized that the C(-1019)G

polymorphism of the 5-HT_{1A} receptor gene is associated with response to treatment with AAPDs in terms of cognitive function governed by frontal lobe function, such as attention. However, there has been no study of the relationship between the C(-1019)G polymorphism and the ability of antipsychotic drugs to treat this specific aspect of cognition. The purpose of this study, therefore, was to determine if AAPDs improve attention more effectively in patients with schizophrenia who have C/C genotype than those who carry the G-allele (C/G or G/G genotype).

MATERIALS AND METHODS

Subjects

Records were obtained from Japanese patients meeting the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision*[37] (DSM-IV-TR) criteria for schizophrenia treated at the University Hospital of Toyama Outpatient Clinic. Diagnosis was made with a structured clinical interview by means of the Structured Clinical Interview for DSM-IV Axis I Disorders.[38] Subjects were diagnosed by a consensus of at least two experienced psychiatrists, as reported previously.[39,40] Patients known to be abusing alcohol or other illicit drugs, or those with epilepsy, brain damage, or neurologic disorders, were excluded from the study. This study was carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained after the explanation of the study. The protocol was approved by Ethical Committee of University of Toyama School of Medicine. At baseline, the subjects had not received any medication for more than 1 month, and were actively psychotic with the Scale for the Assessment of Positive Symptoms (SAPS)[41] (sum of the Global Scales) score of more than 4. SAPS and the Scale for Assessment of Negative symptoms (SANS)[42] were performed by experienced psychiatrists who were not informed of medication status. Interrater reliability was >80%.[39,40]

Immediately after the baseline assessment, antipsychotic medication with olanzapine (once daily) or perospirone (an atypical antipsychotic drug marketed in Japan[40]) (four times/day) was started and titrations were completed during the initial 6 weeks, based on previous reports[39,40] (see Table 1 for dosage). The choice of medication was at the discretion of treating psychiatrists, who adjusted the dose to optimize improvement in psychopathology, while attempting to keep the side effects of the drug tolerable. Concomitant medications were restricted to small doses of benzodiazepines (diazepam equivalent doses of <6 mg/day). Three months after the start of the treatment, clinical assessments were repeated.

Based on the a priori hypothesis, genotype effect on the change of the SANS-Attention subscale score, in addition to the SAPS-Total and SANS-Total scores, was analyzed.

Genotyping

Genotyping was performed by technicians blinded to clinical status. DNA was extracted from peripheral blood samples following standard procedures. Polymerase chain reaction (PCR) was carried out using Taq DNA polymerase (LaboPass™ HS-Taq, LaboPass, Seoul, Korea). The C(-1019)G promotor region polymorphism of the 5-HT1A receptor gene was identified by following pair of primers (forward primer: 5'CCTCTCCTTGTCCTTTGA3'; reverse primer: 5'GTCAGACCAAGGTTGTAAC3'). PCR amplification for a total 30 μL reaction volume contained 20 ng genomic DNA, 0.2 μL HS-Taq (2.5 U/μL), 2.4 μL dNTPs, 1.0 μL of each primer.

The reaction product underwent electrophoresis on a 2.0% agarose gel, from which alleles were identified.

Data Analysis

Statistical analysis was carried out using SPSS version 18 (IBM, Chicago, IL, USA). A *t*-test (two-tailed) was conducted to investigate the effects of genotype on changes of psychopathology and attention scores. Significance was considered when $P<0.05$. Data are expressed as mean±SD.

RESULTS

Clinical data from 30 patients were available for analysis (Table 1). For these subjects, SAPS-Total (sum of the Global Scales), SANS-Total (sum of the Global Scales), and SANS-Attention subscale scores at baseline were 5.6±4.2, 11.6±3.7, and 1.8±1.3, respectively. Seventeen subjects had the CC genotype, three had the GG genotype, and 10 were heterozygous.

Owing to the small number of the GG group, statistical analyses were conducted between subjects with the CC genotype versus those with the GG genotype or heterozygous genotype.

In all subjects, 3-month treatment with antipsychotic drugs was found to significantly improve positive symptoms, as evaluated by the SAPS ($t=4.4$, $P<0.001$) and negative symptoms, as evaluated by SANS ($t=3.7$, $P=0.001$); while attention, as measured by the SANS-Attention subscale score, was not affected ($t=1.5$, P=nonsignificant). As shown in Table 1, there were no significant differences in the degree of change in SAPS and SANS-Total scores between the CC genotype group and (C/G plus G/G) combined group, although the former group showed a numerically better response to treatment. On the other hand, the CC genotype group showed a significantly better response in terms of attention, as compared to the (C/G plus G/G) group (Table 1).

Table 1. Demographic data and influence of the serotonin 5-HT_{1A} receptor C(-1019)G polymorphism on the effect of antipsychotic drugs on symptom changes in patients with schizophrenia.

	5-HT_{1A} receptor genotypes, mean±SD		*P* value
	C/C	C/G or G/G	
Sex, male/female	12/5	7/6	NS
Age, year	31.9±11.1	31.2 ±11.3	NS
Onset of illness, year	21.4±7.5	25.6±8.2	NS
Neuroleptic dose*	3.7±4.2	2.5±1.5	NS
Score change			
ΔSAPS	−3.1±3.3	−2.4±3.0	0.64
ΔSANS	−3.2±3.7	−2.1±3.4	0.22
ΔAttention	−1.1±1.3	0.0±1.7	0.016

Attention=SANS-Attention subscale score; NS=nonsignificant; SANS=Scale for the Assessment of Negative Symptoms–Sum of the Global Scales; SAPS=Scale for the Assessment of Positive Symptoms–Sum of the Global Scales; Δ=change in.
*Risperidone equivalent dose (mg/day) at 3 months.

DISCUSSION

Consistent with the a priori hypothesis, the results of this study suggest antipsychotic drugs ameliorate impaired attention of schizophrenia more effectively in patients having the C/C genotype at C(-1019)G of 5-HT_{1A} receptors than those having the G/G or G/C genotype. The presence of the G-allele was associated with, on average, no improvement in attention.

To our knowledge, this study is the first to investigate the effect of the C(-1019)G polymorphism on the ability of AAPDs to improve a specific aspect of cognition in schizophrenia, and extends previous findings that the C(-1019)G SNP is associated with a response to treatment with various antipsychotic drugs in terms of negative[22,25] and depressive[22]

symptoms. Specifically, both of these studies[22,25] report that the presence of the G-allele, ie, G/G or G/C genotype, predicts a limited response to treatment with AAPDs. Thus, the results of the present study may provide a rational treatment strategy for attention impairments characteristic of schizophrenia.

It is possible that the increase in somatodendritic 5-HT_{1A} receptor expression associated with the G-allele[43] may mediate decreased efficacy of AAPDs. Also, our findings are in concert with the suggestion that the C(-1019)G polymorphism in the 5-HT_{1A} receptor predicts structural and functional characteristics in cortical regions receiving projection of 5-HT neurons, such as parahippocampal gyrus and prefrontal cortex, as these brain areas are responsible for some of the key domains of cognitive function, eg, verbal learning memory, working memory, attention/information processing, and social cognition.[7,44] Whether the C(-1019)G polymorphism is associated with the ability of antipsychotic drugs to treat other cognitive domains deserves further studies.

The limitations of the present study include a small sample number that might have caused a lack of robust level of significance and variability. For example, it might explain the absence of a significant effect of C(-1019)G SNPs on negative symptoms, in contrast to the results in previous studies.[22,25] Secondly, the measure of attention used here is "nonspecific" and not a cognitive test per se; the use of a specific neuropsychological test should enhance sensitivity and specificity to detect possible changes of attention. Furthermore, the two test drugs, perospirone and olanzapine, have different affinities for 5-HT_{1A} receptors; olanzapine shows minimal direct affinity for these receptors.[45] However, the increase in DA release produced by it is blocked by 5-HT_{1A} antagonists (eg, WAY 100635),[35,36] indicating this antipsychotic drug indirectly stimulates 5-HT_{1A} receptors.[45,46] Pretreatment with WAY 100635 also suppresses the increase in DA concentrations induced by perospirone, an AAPD having a high affinity for 5-HT_{1A} receptors.[47]

CONCLUSION

In conclusion, these results provide additional support to the role of 5-HT_{1A} receptors in some of the cognitive disturbances of schizophrenia, and facilitate the treatment strategy to effectively improve attention. Further studies with a larger number of subjects are warranted.

ACKNOWLEDGMENTS

The authors declare no conflict of interest. Tomiki Sumiyoshi organized the study and wrote the manuscript. Masahiko Tsunoda and Hiroko Itoh performed genotyping and data management. Yuko Higuchi, Toru Itoh, and Tomonori Seo conducted clinical evaluation. Michio Suzuki and Masayoshi Kurachi conducted the literature searches.

This work was supported by grants-in-aid for Scientific Research from Japan Society for the Promotion of Science and grants-in-aid from the Ministry of Health, Labour and Welfare, Japan. These funding bodies had no further role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report.

REFERENCES

1. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the "right stuff"? Schizophr Bull. 2000;26:119-136.

2. McGurk SR, Meltzer HY. The role of cognition in vocational functioning in schizophrenia. Schizophr Res. 2000;45:175-184.

3. Sumiyoshi T, Park S, Jayathilake K, Roy A, Ertugrul A, Meltzer HY. Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res. 2007;95:158-168.

4. Millan MJ. Improving the treatment of schizophrenia: focus on serotonin (5-HT)(1A) receptors. J Pharmacol Exp Ther. 2000;295:853-861.

5. Bantick RA, Deakin JF, Grasby PM. The 5-HT1A receptor in schizophrenia: a promising target for novel atypical neuroleptics? J Psychopharmacol. 2001;15:37-46.

6. Meltzer HY, Sumiyoshi T. Does stimulation of 5-HT(1A) receptors improve cognition in schizophrenia? Behav Brain Res. 2008;195:98-102.

7. Sumiyoshi T, Bubenikova-Valesova V, Horacek J, Bert B. Serotonin1A receptors in the pathophysiology of schizophrenia: development of novel cognition-enhancing therapeutics. Adv Ther. 2008;25:1037-1056.

8. Lesch KP, Gutknecht L. Focus on The 5-HT1A receptor: emerging role of a gene regulatory variant in psychopathology and pharmacogenetics. Int J Neuropsychopharmacol. 2004;7:381-385.

9. Drago A, Ronchi DD, Serretti A. 5-HT1A gene variants and psychiatric disorders: a review of current literature and selection of SNPs for future studies. Int J Neuropsychopharmacol. 2008;11:701-721.

10. Hashimoto T, Nishino N, Nakai H, Tanaka C. Increase in serotonin 5HT1A receptors in prefrontal and temporal cortices of brains from patients with chronic schizophrenia. Life Sci. 1991;48:355-363.

11. Sumiyoshi T, Stockmeier CA, Overholser JC, Dilley GE, Meltzer HY. Serotonin1A receptors are increased in postmortem prefrontal cortex in schizophrenia. Brain Res. 1996;708:209-214.

12. Kasper S, Tauscher J, Willeit M, et al. Receptor and transporter imaging studies in schizophrenia, depression, bulimia and Tourette's disorder--implications for psychopharmacology. World J Biol Psychiatry. 2002;3:133-146.

13. Tauscher J, Kapur S, Verhoeff NP, et al. Brain serotonin 5-HT1A receptor binding in schizophrenia measured by positron emission tomography and [11C]WAY-100635. Arch Gen Psychiatry. 2002;59:514-520.

14. Frankle WG, Lombardo I, Kegeles LS, et al. Serotonin 1A receptor availability in patients with schizophrenia and schizo-affective disorder: a positron emission tomography imaging study with [11C]WAY 100635. Psychopharmacology (Berl). 2006;189:155-164.

15. Lee MA, Meltzer HY. 5-HT(1A) receptor dysfunction in female patients with schizophrenia. Biol Psychiatry. 2001;50:758-766.

16. Sumiyoshi T, Meltzer HY. Serotonin1A receptors in memory function. Am J Psychiatry. 2004;161:1505.

17. Borg J. Molecular imaging of the 5-HT(1A) receptor in relation to human cognition. Behav Brain Res. 2008;195:103-111.

18. Sumiyoshi T, Matsui M, Nohara S, et al. Enhancement of cognitive performance in schizophrenia by addition of tandospirone to neuroleptic treatment. Am J Psychiatry. 2001;158:1722-1725.

19. Sumiyoshi T, Matsui M, Yamashita I, et al. Effect of adjunctive treatment with serotonin-1A agonist tandospirone on memory functions in schizophrenia. J Clin Psychopharmacol. 2000;20:386-388.

20. Harvey PD. Pharmacological cognitive enhancement in schizophrenia. Neuropsychol Rev. 2009;19:324-335.

21. Lane HY, Chang YC, Chiu CC, Chen ML, Hsieh MH, Chang WH. Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. Am J Psychiatry. 2002;159:1593-1595.

22. Reynolds GP, Arranz B, Templeman LA, Fertuzinhos S, San L. Effect of 5-HT1A receptor gene polymorphism on negative and depressive symptom response to antipsychotic treatment of drug-naive psychotic patients. Am J Psychiatry. 2006;163:1826-1829.

23. Reynolds GP, Yao Z, Zhang X, Sun J, Zhang Z. Pharmacogenetics of treatment in first-episode schizophrenia: D3 and 5-HT2C receptor polymorphisms separately associate with positive and negative symptom response. Eur Neuropsychopharmacol. 2005;15:143-151.

24. Richtand NM, Welge JA, Logue AD, Keck PE, Jr., Strakowski SM, McNamara RK. Dopamine and serotonin receptor binding and antipsychotic efficacy. Neuropsychopharmacol. 2007;32:1715-1726.

25. Wang L, Fang C, Zhang A, et al. The --1019 C/G polymorphism of the 5-HT1A receptor gene is associated with negative symptom response to risperidone treatment in schizophrenia patients. J Psychopharmacol. 2008;22:904-909.

26. Huang YY, Battistuzzi C, Oquendo MA, et al. Human 5-HT1A receptor C(-1019)G polymorphism and psychopathology. Int J Neuropsychopharmacol. 2004;7:441-451.

27. Kishi T, Tsunoka T, Ikeda M, et al. Serotonin1A receptor gene is associated with Japanese methamphetamine-induced psychosis patients. Neuropharmacol. 2010;58:452-456.

28. Serretti A, Artioli P, Lorenzi C, Pirovano A, Tubazio V, Zanardi R. The C(-1019)G polymorphism of the 5-HT1A gene promoter and antidepressant response in mood disorders: preliminary findings. Int J Neuropsychopharmacol. 2004;7:453-460.

29. Lemonde S, Du L, Bakish D, Hrdina P, Albert PR. Association of the C(-1019)G 5-HT1A functional promoter polymorphism with antidepressant response. Int J Neuropsychopharmacol. 2004;7:501-506.

30. Hong CJ, Chen TJ, Yu YW, Tsai SJ. Response to fluoxetine and serotonin1A receptor (C-1019G) polymorphism in Taiwan Chinese major depressive disorder. Pharmacogenomics J. 2006;6:27-33.

31. Yu YW, Tsai SJ, Liou YJ, Hong CJ, Chen TJ. Association study of two serotonin1A receptor gene polymorphisms and fluoxetine treatment response in Chinese major depressive disorders. Eur Neuropsychopharmacol. 2006;16:498-503.

32. Baune BT, Hohoff C, Roehrs T, Deckert J, Arolt V, Domschke K. Serotonin receptor 1A-1019C/G variant: impact on antidepressant pharmacoresponse in melancholic depression? Neurosci Lett. 2008;436:111-115.

33. Chung YC, Li Z, Dai J, Meltzer HY, Ichikawa J. Clozapine increases both acetylcholine and dopamine release in rat ventral hippocampus: role of 5-HT1A receptor agonism. Brain Res. 2004;1023:54-63.

34. Sato M, Ago Y, Koda K, et al. Role of postsynaptic serotonin1A receptors in risperidone-induced increase in acetylcholine release in rat prefrontal cortex. Eur J Pharmacol. 2007;559:155-160.

35. Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY. 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5- HT1A receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem. 2001;76:1521-1531.

36. Diaz-Mataix L, Scorza MC, Bortolozzi A, Toth M, Celada P, Artigas F. Involvement of 5-HT1A receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. J Neurosci. 2005;25:10831-10843.

37. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Text Revision) . Washington DC: APA; 2000.

38. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders. New York: New York State Psychiatric Institute; 1997.

39. Higuchi Y, Sumiyoshi T, Kawasaki Y, Matsui M, Arai H, Kurachi M. Electrophysiological basis for the ability of olanzapine to improve verbal memory and functional outcome in patients with schizophrenia: A LORETA analysis of P300. Schizophr Res. 2008;101:320-330.

40. Sumiyoshi T, Higuchi Y, Itoh T, et al. Effect of perospirone on P300 electrophysiological activity and social cognition in schizophrenia: a three-dimensional analysis with sLORETA. Psychiatry Res Neuroimag 2009;172:180-183.

41. Andreasen NC. Scale for the Assessment of Positive Symptoms (SAPS). Iowa City: University of Iowa; 1983.

42. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City: University of Iowa; 1983.

43. Parsey RV, Oquendo MA, Ogden RT, et al. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. Biol Psychiatry. 2006;59:106-113.

44. Erdmann J, Shimron-Abarbanell D, Rietschel M, et al. Systematic screening for mutations in the human serotonin-2A receptor gene: identification of two naturally occurring receptor variants and association analysis in schizophrenia. Hum Genet. 1996;97:614-619.

45. Sumiyoshi T. A possible dose-side effect relationship of antipsychotic drugs: Relevance to cognitive function in schizophrenia. Expert Rev Clin Pharmacol. 2008;1:791-802.

46. Sumiyoshi T, Matsui M, Yamashita I, et al. The effect of tandospirone, a serotonin1A agonist, on memory function in schizophrenia. Biol Psychiatry. 2001;49:861-868.

47. Yoshino T, Nishijima K, Shioda K, Yui K, Katoh S. Perospirone, a novel atypical antipsychotic drug, potentiates fluoxetine-induced increases in dopamine levels via multireceptor actions in the rat medical prefrontal cortex. Neurosci Lett. 2004;24:16-21.

Psychopharmacology (2010) 212:267–276
DOI 10.1007/s00213-010-1951-3

ORIGINAL INVESTIGATION

Effect of tandospirone, a serotonin-1A receptor partial agonist, on information processing and locomotion in dizocilpine-treated rats

Vera Bubenikova-Valesova · Jan Svoboda · Jiri Horacek · Tomiki Sumiyoshi

Received: 4 February 2010 / Accepted: 3 July 2010 / Published online: 31 July 2010

Abstract
Rationale Augmentation therapy with serotonin-1A receptor (5-HT1A) partial agonists has been suggested to ameliorate psychotic symptoms in patients with schizophrenia.
Objective and methods The objective of the present study was to examine the effect of repeated administration of tandospirone (0.05 and 5 mg/kg) on locomotor activity in a novel environment and on sensorimotor gating in rats treated with the N-*methyl*-D-aspartate receptor antagonist MK-801, which has been used in animal models of schizophrenia. Furthermore, we sought to determine whether the effect of tandospirone on these behavioural measures is blocked by WAY 100635 (0.3 mg/kg), a 5-HT1A receptor antagonist, and whether there is an interaction between haloperidol (0.1 mg/kg; a dopamine-D2 receptor antagonist) and tandospirone.
Results Tandospirone at 5 mg/kg, but not 0.05 mg/kg, decreased locomotor activity in saline or MK-801-treated rats, which were not affected by co-treatment with WAY 100635. Haloperidol decreased locomotion both in saline and MK-801-treated animals, and this effect was not evident in the latter group receiving the higher dose of tandospirone. Tandospirone (5 mg/kg)-induced disruption of sensorimotor gating in saline or MK-801-treated animals was reversed by WAY-100635, but not by haloperidol.
Conclusions These findings suggest that behavioural changes induced by tandospirone are not fully blocked by 5-HT1A antagonists and that tandospirone (5 mg/kg) potentiates the effect of MK-801. Overall, these findings point to an interaction between NMDA and 5-HT_{1A} receptors. Part of the effect of tandospirone on locomotor activity may be mediated by the actions of its active metabolites on other neurotransmitter systems.

Keywords Tandospirone · Schizophrenia · NMDA receptor · MK-801 · Locomotion · PPI · Haloperidol

V. Bubenikova-Valesova · J. Horacek
Department of Brain Pathophysiology and Biochemistry,
Prague Psychiatric Centre,
Prague, Czech Republic

J. Svoboda
Department of Neurophysiology of Memory and Computational Neuroscience, Institute of Physiology,
Czech Academy of Sciences,
Prague, Czech Republic

J. Horacek
Third Faculty of Medicine, Charles University,
Prague, Czech Republic

T. Sumiyoshi
Department of Neuropsychiatry, University of Toyama
Graduate School of Medicine and Pharmaceutical Sciences,
Toyama, Japan

V. Bubenikova-Valesova (✉)
Laboratory of Biochemistry and Brain Pathophysiology,
Prague Psychiatric Centre,
Ústavní 91,
Prague 8-Bohnice 181 03, Czech Republic
e-mail: bubenikova@pcp.lf3.cuni.cz

Introduction

Serotonin (5-HT) receptors have been suggested as providing potential roles in psychosis and cognition via an influence on various neurotransmitter systems. Among the 5-HT receptor subtypes, 5-HT1A receptors exist as autoreceptors on raphe cell bodies and modify endogenous 5-HT synthesis and release (Hjorth and Sharp 1991; Sharp and

Foster 1991), and they also exist as postsynaptic receptors which directly affect the activity of non-serotonergic neurons in a variety of brain areas (Tanaka et al. 1995).

Tandospirone, an azapirone, is a selective 5-HT1A partial agonist and displays approximately 60% of the effect of the full agonist 8-OH-DPAT (Hamik et al. 1990). Anxiolytic properties of tandospirone, as marketed in Japan, have been demonstrated in human and animal studies (Nishikawa et al. 2007; Nishitsuji et al. 2004; Nishitsuji et al. 2006; Sugimoto et al. 1998). Furthermore, Sumiyoshi and colleagues (Bubenikova-Valesova et al. 2007b; Sumiyoshi et al. 2000; Sumiyoshi et al. 2001b; Sumiyoshi et al. 2001a; Sumiyoshi et al. 2007a) conducted a series of studies on the effect of the addition of tandospirone to ongoing treatment with small to moderate doses of antipsychotic drugs on cognitive function in patients with schizophrenia. Specifically, they found that the addition of tandospirone (30 mg/day) to the typical antipsychotic drug regime for 4–6 weeks improved cognitive function in patients with schizophrenia (Bubenikova-Valesova et al. 2007b; Sumiyoshi et al. 2000; Sumiyoshi et al. 2001b; Sumiyoshi et al. 2001a; Sumiyoshi et al. 2007a).

The glutamatergic neurotransmitter system has been suggested as playing an important role in the aetiopathogenesis of schizophrenia, based on findings on various aspects of neural substrates ranging from molecular interactions to the neuronal network in the human brain (Goff and Coyle 2001; Kristiansen et al. 2007). Moreover, administration of non-competitive antagonists of N-*methyl*-D-aspartate (NMDA) glutamate receptors (phencyclidine, ketamine, and MK-801) has been reported to induce behavioural abnormalities related to symptoms of schizophrenia, such as impairment of information processing and attention, as well as hyperlocomotion in response to a novel environment, which are all ameliorated by antipsychotic use (Bubenikova-Valesova et al. 2008a; Amitai et al. 2007; Bubenikova-Valesova et al. 2008a; Bubenikova et al. 2005; Bubenikova-Valesova et al. 2008b).

In this study, we investigated the effect of repeated administration of tandospirone on deficits in sensorimotor gating and locomotion in rats treated with the NMDA receptor antagonist MK-801. Sensorimotor gating was measured by prepulse inhibition (PPI) of the acoustic startle response. This task consisted of a brief presentation of a high intensity sound stimulus to cause a normal startle reflex response. When this stimulus is preceded by a weak, non-startling stimulus (a prepulse), the subsequent startle response is attenuated (Koch 1999). Deficits in sensorimotor gating have been observed in patients with several neuropsychiatric disorders, including schizophrenia and bipolar disorder (Gogos et al. 2009; Swerdlow et al. 2006). Locomotor activity in response to a novel environment after administration of NMDA antagonists has been widely used in modelling the positive symptoms of schizophrenia. Although hyperlocomotion is not entirely dependent on dopaminergic activation, it is blocked by antipsychotics (van den Buuse 2010).

It was reported that haloperidol blocks the effect of 5-HT1A agonists on information processing (van den Buuse and Gogos 2007). In other studies, 5-HT1A agonists were shown to ameliorate haloperidol-induced catalepsy (Ohno et al. 2008; Ohno et al. 2009). To the best of our knowledge, there is little information on whether 5-HT1A partial agonists, such as tandospirone, interact with D2 receptors in a similar way to the full agonists at 5-HT1A receptors or not. There is also a paucity of animal experiments to determine whether the combination of haloperidol with tandospirone shows an antipsychotic-like profile, despite clinical observations indicating an advantage of augmentation therapy with partial 5-HT1A agonists in patients treated with typical antipsychotic drugs, such as haloperidol.

The principal purpose of this study was to test the hypothesis that moderate stimulation of 5-HT1A receptors with or without the influence of antipsychotic drugs would ameliorate sensorimotor deficits in psychosis-like states (Bubenikova-Valesova et al. 2007b; Sumiyoshi et al. 2008). Furthermore, we sought to determine whether the effect of tandospirone on these behavioural measures is blocked by WAY 100635, an antagonist at 5-HT1A receptors, and whether an interaction occurs between tandospirone and the typical antipsychotic drug haloperidol, which is a dopamine-D2 receptor antagonist.

Materials and methods

Drugs

The treatment regimen with MK-801 was based on our previous report (Bubenikova-Valesova et al. 2007b). The N-*methyl*-D-aspartate receptor antagonist MK-801 (Sigma-Aldrich, Czech Republic; Dizocilpine maleate; [5R,10S]-[+]-5-*methyl*-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine), at a dose of 0.1 mg/kg, was dissolved in saline. The rats received an i.p. injection of MK-801 at a volume of 2 ml/kg for 4 days. The last injection was applied i.p. 15 min prior to the tests. Tandospirone (a gift from Dainippon Sumitomo Pharma Co., Ltd., Japan) was dissolved in saline at a volume of 2 ml/kg. The rats received a s.c. injection of tandospirone at 0.05 or 5 mg/kg for 4 days and a s.c. injection 30 min prior to the tests. Haloperidol (Sigma-Aldrich) at 0.1 mg/kg was dissolved in 15 μl of acetic acid and was added to saline at a volume of 2 ml/kg. The haloperidol (s.c.) was adminis-

tered 60 min before the experiments. The WAY 100635 (0.3 mg/kg, s.c.; Sigma-Aldrich, Czech Republic) (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-ethyl]-N-(2-pyridinyl) cyclohexanecarboxamide) was applied 30 min before the experiments. All animals received the same volume of vehicle per 1 kg of body weight. The control animals received the corresponding vehicle.

Animals

Male Wistar rats (200–250 g, Hannover breed, Konárovice, Czech Republic; n=356) were used in this study. Two rats per cage were housed in a temperature-controlled room (21–22°C), with a 12:12 h light/dark regime (lights on at 7:00 a.m.) with free access to food (ST-1 diet) and water. Each rat was only tested once. All manipulations were performed according to the Guidelines of the European Union Council (86/609/EU) and followed the instructions of the National Committee for the Care and Use of Laboratory Animals.

Apparatus and behavioural procedures

Locomotor activity in a novel environment

Locomotor activity, expressed as total distance travelled during 30 min in a box (68×68×30 cm) located in a soundproof room, was measured using a video tracking system for automation of the behavioural experiments (Noldus, Netherlands, EthoVision Colour Pro-Version 3.1), as described previously (Bubenikova-Valesova et al. 2007b).

Prepulse inhibition of acoustic startle response

All testing occurred within a startle chamber (SR-LAB, San Diego Instruments, California, USA). The rats were initially tested by a short session (5 min acclimatisation period plus five single stimuli; 120 dB) 2 days before the experiment. Briefly, the acclimatisation period (75 dB) was presented alone for 5 min. After this, the test began with five initial startle stimuli (125 dB) followed by four different trial types presented in a pseudorandom order: (1) single pulse: 125 db broadband burst, 40 ms duration; (2) prepulse: 13 dB, 20 ms duration above the background noise 100 ms before the onset of the pulse alone; (3) prepulse alone: 13 dB, 20 ms duration above the background noise; (4) no stimulus. A total of five presentations for each trial type were given with an inter-stimulus interval varying from 25 to 30 s. The PPI was calculated as the difference between the average values of the single pulse and prepulse-pulse trials and was expressed as a percentage of the PPI [100 − (mean response for prepulse − pulsetrials/startle response forsinglepulse trials) × 100]. Data from the four single pulse trials at the beginning of the test session were not included in the calculation of the PPI and acoustic startle response values. Animals showing average startle amplitudes lower than 10 mV were removed from the calculation of the PPI and were marked as non-responders (about 3% of the total number). The number of removed animals did not differ between the treatment groups.

Data analysis

Data are presented as means±SEM. Data from the PPI, startle response and open-field locomotion were first evaluated using three-way analysis of variance (ANOVA) with the dose of tandospirone (0, 0.05, 5 mg/kg) as the factor level and the co-treatment agents MK-801 and WAY100635 (or haloperidol) as between-subject factors. Then, separate two-way ANOVAs were conducted for groups with and without MK-801 treatment, followed by Tukey's Honestly Significant Difference (HSD) post-hoc test. A separate evaluation of tandospirone and MK-801 treatment was also performed using two-way ANOVA. Statistical significance was accepted at $p<0.05$ in all instances. We used ten animals per group in all experiments except for the WAY 100635/MK-801 group (n=9) and the tandospirone 0.05 mg/kg/WAY 100635/MK-801 group (n=8) in the open-field locomotion.

Results

Effect of sub-chronic administration of MK-801 and tandospirone on the startle response and PPI

Two-way ANOVA found main effects of tandospirone [$F(2,54)=17.28$, $p<0.0001$] and MK-801 [$F(1,54)=7.14$, $p<0.001$] on PPI, but the interaction between them was not significant $F(2,54)=2.68$, $p<0.0001$]. Tukey's HSD post-hoc test revealed tandospirone at 5 mg/kg decreased PPI both with and without MK-801 co-treatment ($p<0.01$) (Fig. 1a).

Tandospirone [$F(2,54)=8.38$, $p<0.001$], but not MK-801 [$F(1,54)=0.01$, NS], was found to have an effect on startle amplitudes; tandospirone vs. MK-801 interaction was not significant [$F(2,54)=0.33$, NS] (Fig. 1b).

Effect of sub-chronic administration of MK-801 and tandospirone on locomotor activity

As two-way ANOVA demonstrated, locomotor activity was affected by both tandospirone [$F(2,54)=13.88$, $p<0.0001$] and MK-801 [$F(1,54)=4.56$, $p<0.05$]; interactions between

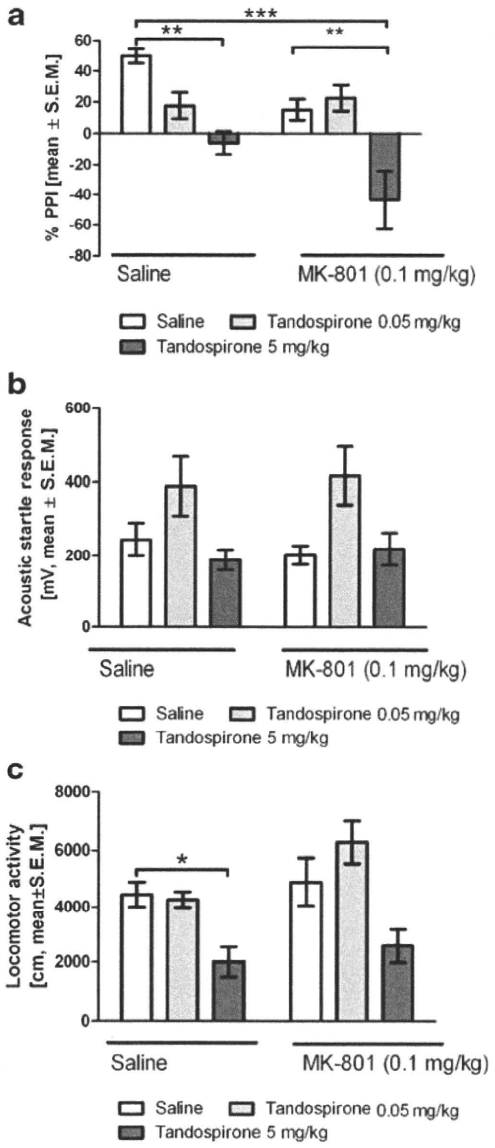

Fig. 1 Effect of sub-chronic administration of tandospirone on schizophrenia-like behaviour induced by MK-801. Tandospirone decreased PPI with and without MK-801 (**a**). The startle response was increased by tandospirone at 0.05 mg/kg in saline and in MK-801-treated rats (**b**). Tandospirone (5 mg/kg) decreased locomotor activity in saline and MK-801-treated rats (**c**). *$p<0.05$; ***$p<0.001$ by Tukey's post-hoc test

the two factors were insignificant [F(2,54)=1.06, NS]. Tukey's HSD post-hoc test found that tandospirone at 5 mg/kg suppressed locomotion ($p<0.05$) (Fig. 1c).

The 5-HT1A receptor antagonist (WAY 100635) blocked the effect of tandospirone on PPI and the startle response with/without MK-801 co-treatment

Three-way ANOVA found significant effects of tandospirone [F(2,107)=18.65, $p<0.0001$], MK-801 [F(1,107)=15.3, $p<0.01$] and WAY 100635 [F(1,107=17.22, $p<0.0001$] on PPI, while tandospirone vs. MK-801 vs. WAY 100635 interaction was not significant [F(2,107)=1.73, NS]. Moreover, there were also significant tandospirone vs. MK-801 [F(2,107=6.09, $p<0.01$] and tandospirone vs. WAY 100635 [F(2, 107=9.31, $p<0.001$], but not MK-801 vs.WAY 100635 interactions.

Subsequent two-way ANOVAs were separately conducted to assess the groups with and without MK-801. The main effects of tandospirone [F(2,53)=23.13, $p<0.0001$] and WAY 100635 [F(1,53)=8.91, $p<0.01$], but not their interaction [F(2,54)=2.32, NS], on PPI were significant among the groups without MK-801. Tukey's HSD post-hoc test revealed a progressive disruption of PPI with increasing dose of tandospirone (0.05 mg/kg, $p<0.05$, compared to the saline/saline group; 5 mg/kg, $p<0.001$). This disruption was partially reversed by WAY 100635 only at 5 mg/kg tandospirone ($p<0.01$, compared with the tandospirone at 5 mg/kg alone group) (Fig. 2a).

Among the MK-801 co-treated groups, tandospirone was found to potentiate MK-801-induced PPI impairment [F(2,54)=7.27, $p<0.01$], while WAY 100635 blocked this effect [F(1,54)=8.95, $p<0.01$]. There was also a significant tandospirone vs. WAY 100635 interaction [F(2,54)=7.12, $p<0.01$]. The post-hoc test revealed that tandospirone potentiated the effect of MK-801 only at 5 mg/kg ($p<0.001$), and that this potentiation was fully blocked by WAY 100635 $p<0.001$) (Fig. 2a).

When analysing data from the startle response, three-way ANOVA did not find the following interactions significant tandospirone vs. MK-801 vs. WAY 100635 [F(2,108)=0.17, NS], tandospirone vs. MK-801 [F(2,108=0.58, NS], and MK-801 vs. WAY 100635 [F(2,108)=0.18, NS], contrasting with significant tandospirone vs. WAY 100635 [F(2,108=6.94, $p<0.01$] interaction. Although ANOVA rejected the main effect of MK-801 [F(1,108)=0.44, NS], it confirmed the effects of tandospirone [F(2,108)=9.35, $p<0.001$] and WAY 100635 [F(2,108)=61.42, $p<0.0001$].

The separate two-way ANOVA tests revealed significant effects of tandospirone [F(2,54)=3.49, $p<0.05$] and WAY 100635 [F(1,54)=33.34, $p<0.0001$], as well as a significant interaction between them [F(2,54)=3.55, $p<0.05$], in rats without MK-801 treatment. Application of 0.5 mg/kg tandospirone moderately, but not significantly, increased the startle response compared to saline/saline rats. This response was significantly reduced by co-treatment with WAY 100635 (Fig. 2b).

The two-way ANOVA test for rats with MK-801 treatment also revealed significant effects of tandospirone [F(2,54)=6.51, $p<0.01$] and WAY 100635 [F(1,54)=28.14, $p<0.0001$], as well as a significant interaction between them [F(2,54)=3.56, $p<0.05$]. In this case, application of 0.5 mg/kg tandospirone led to a significantly stronger startle response compared to

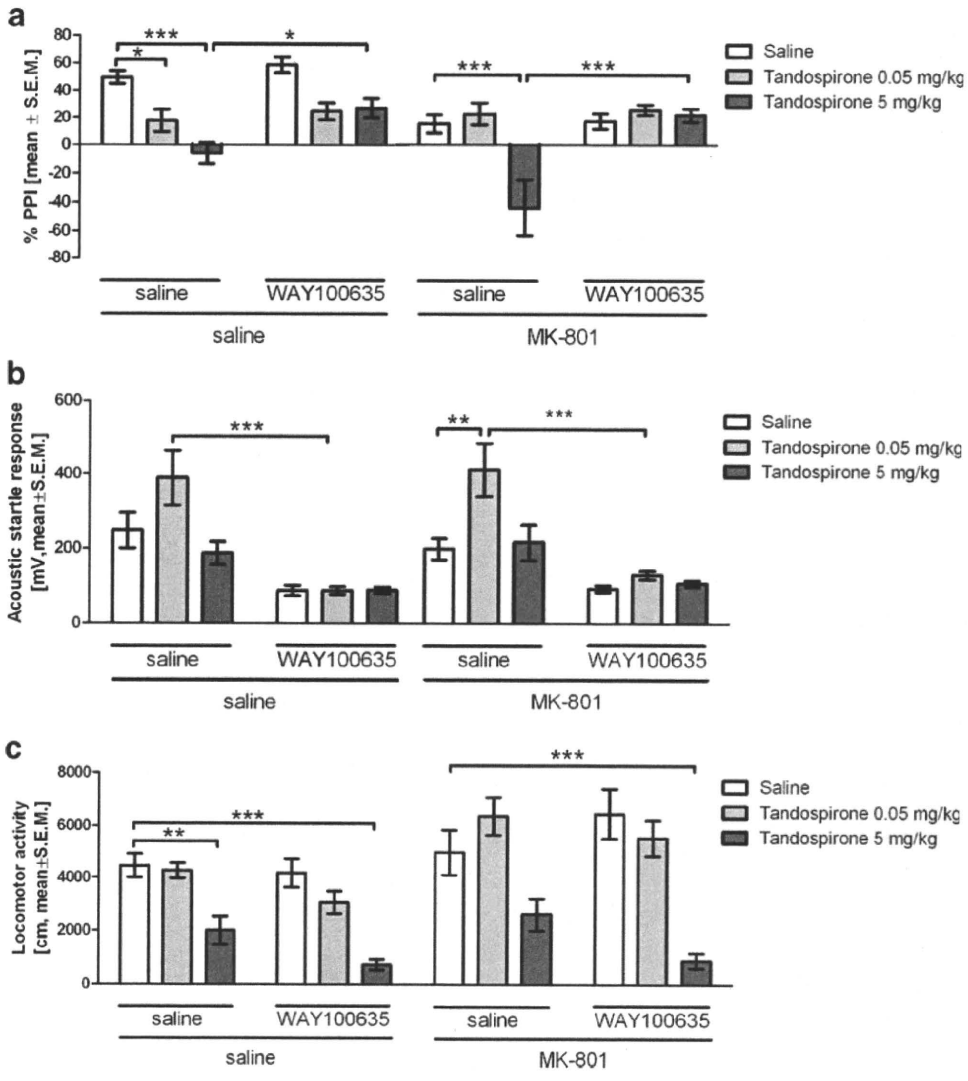

Fig. 2 The effect of WAY 100635 (5-HT1A antagonist) on behaviour induced by tandospirone. WAY 100635 (0.3 mg/kg) blocked the effect of tandospirone (5 mg/kg) with and without MK-801 (**a**). WAY 100635 blocked the effect of tandospirone (0.05 mg/kg) on the startle response with and without MK-801 (**b**). WAY 100635 did not inhibit hypolocomotion induced by tandospirone (5 mg/kg). *$p<0.05$; **$p<0.01$; ***$p<0.001$ by Tukey's post-hoc test

saline/saline rats, which was fully blocked by WAY 100635 (Fig. 2b).

Effect of the 5-HT1A receptor antagonist (WAY 100635) on locomotor activity after co-administration of tandospirone with/without MK-801 co-treatment

Three-way ANOVA conducted on locomotor activity revealed that the following interactions were not significant, tandospirone vs. MK-801 vs. WAY 100635 [F(2,105)= 0.91, NS], tandospirone vs. MK-801 [F(2,105=2.58, NS], and MK-801 vs. WAY 100635 [F(2,105)=0.74, NS]. On the contrary, a significant interaction was found for tandospirone vs. WAY 100635 [F(2,105=3.57, $p<0.05$] interaction as well as main effects of tandospirone [F (2,105)=44.99, $p<0.0001$] and MK-801 [F(1,105)=15.22, $p<0.001$], but not WAY 100635 [F(1,105=3.6, NS].

Subsequent two-way ANOVAs were conducted to assess groups with and without MK-801 separately. Administration of tandospirone decreased locomotion [F(2,54)=26.52, $p<0.0001$)] and WAY 100635 potentiated this effect [F (1,54)=7.04, $p<0.05$; tandospirone vs. WAY 100635 interaction F(2,54)=0.86, NS] in non-MK-801-treated rats. Post-hoc analysis indicated tandospirone (5 mg/kg) alone ($p<0.01$) or in combination with WAY 100635 ($p<0.001$) decreased locomotion compared to the saline/saline group.

Among the MK-801 co-treated groups, two-way ANOVA revealed that tandospirone [F(2,51)=22.1, $p<0.0001$], but not WAY 100635 [F(1,51)=0.35, NS], affected locomotor activity. The interaction between them was not significant [F(2,51)=2.68, NS]. Tukey's HSD post-hoc test revealed that rats treated with MK-801+tandospirone (5 mg/kg)+WAY 100635 ($p<0.01$) walked less than saline/MK-801 controls (Fig. 2c).

Haloperidol had no effect on tandospirone or the startle response and PPI with/without MK-801 co-treatment

Three-way ANOVA on startle response data demonstrated that the following interactions were not significant tandospirone vs. MK-801 vs. haloperidol [F(2,108)=1.02, NS]; tandospirone vs. MK-801 [F(2,108)=1.91, NS]; tandospirone vs haloperidol [F(2,108)=1.02, NS]; and MK-801 vs. haloperidol [F(1,108)=0.99, NS]. Whereas the analysis revealed a significant effect of tandospirone [F(2,108)=11.4, $p<0.0001$], the effects of MK-801 [F(1,108)=1.38,NS] and haloperidol [F(1,108=0.99, NS] remained insignificant.

We examined interactions between tandospirone and haloperidol on PPI in rats with/without MK-801 co-treatment. Three-way ANOVA indicated a significant interaction between tandospirone and haloperidol interaction [F(2,107)=3.18, $p<0.05$] while tandospirone vs. MK-801 vs. haloperidol [F(2,107)=2.94, NS], tandospirone vs. MK-801 [F(2,107)=1.86, NS], and MK-801 vs. haloperidol interactions [F(1,107)=0.003, NS] were not significant. Moreover, there were main effects of tandospirone [F(2,107)=12.0, $p<0.0001$] and MK-801 [F(1,107)=11.72, $p<0.001$], but not haloperidol [F(1,107=0.36, NS].

In the rats that were not given MK-801, two-way ANOVA revealed a significant effect of tandospirone [F(2,54)=16,24, $p<0.001$] but not haloperidol [F(1,54)=0.38, NS] and the interaction between these two was also not significant [F(2,54)=1.05, NS]. Tukey's HSD post-hoc test revealed that tandospirone at 5 mg/kg reduced PPI with ($p<0.01$) and without ($p<0.001$) co-treatment with haloperidol (Fig. 3a).

The interaction between tandospirone and haloperidol on PPI was significant in MK-801-treated rats [F(2,53)=3.79, $p<0.05$]. Tandospirone at a dose of 5 mg/kg worsened MK-801-induced PPI impairment ($p<0.05$), and haloperidol completely blocked tandospirone/MK-801-induced PPI disruption ($p<0.05$). There was also a significant main effect of tandospirone [F(2,53)=3.18, $p<0.05$], but not haloperidol [F(1,53)=0.10, NS] on PPI (Fig. 3a).

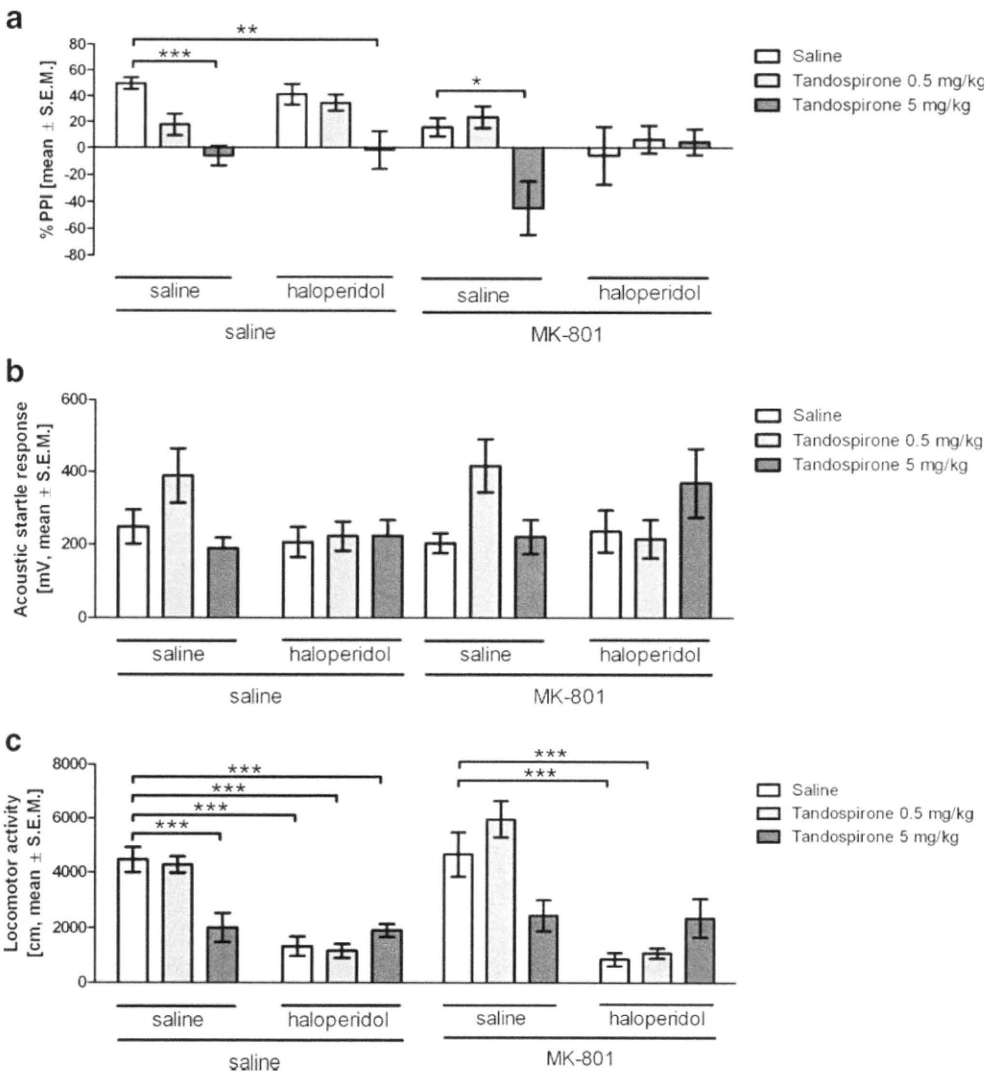

Fig. 3 The effect of haloperidol (D2 antagonist) on behaviour induced by tandospirone. Haloperidol disrupted PPI. Haloperidol did not block the disruption in PPI by tandospirone/MK-801 (**a**). Haloperidol did not change the startle response in combination with tandospirone (**b**). Haloperidol worsened hypolocomotion induced by tandospirone (0.05 mg/kg), but not at a dose of 5 mg/kg

Neither tandospirone [F(2,54)=2.41, NS] nor haloperidol [F(1,54)=2.20, NS] treatment yielded any effect in rats without MK-801 co-treatment. Moreover, the interaction between tandospirone and haloperidol interaction was not significant [F(2,54)=2.26, NS]. Likewise, tandospirone [F(2,54)=1.33, NS] and haloperidol [F(1,54)=0.02, NS] did not show a significant effect on the startle response in rats co-treated with MK-801. Although the interaction between tandospirone and haloperidol was significant [F(2,54)=4.08, $p<0.05$], Tukey's HSD post-hoc test did not identify any difference between the groups (Fig. 3b).

Effect of haloperidol on locomotor activity after co-administration of tandospirone with/without MK-801 treatment

When analysing locomotor activity in the open field, three-way ANOVA did not identify any significant interactions between tandospirone vs. MK-801 vs. haloperidol [F(2,107)=1.06, NS], tandospirone vs. MK-801 [F(2,107)=0.98, NS], or MK-801 vs. haloperidol [F(1,107)=2.81, NS]. However, the interaction between tandospirone and haloperidol interaction was significant [F(2,107)=18.93, $p<0.0001$]. Furthermore, main effects of haloperidol [F(1,107)=81.01, $p<0.0001$] and tandospirone [F(2,107)=3.89, $p<0.05$], but not MK-801 [F(1,107)=3.33, NS], were significant.

Subsequent two-way ANOVA revealed significant effects of tandospirone [F(2,54)=3,68, $p<0.05$] and haloperidol [F(1,54)=49,86, $p<0.0001$], and a significant interaction between these [F(2,54)=11,27, $p<0.0001$] on locomotion in rats without MK-801. Tukey's HSD post-hoc test found that tandospirone at a dose of 5 mg/kg decreased locomotor activity compared with the controls ($p<0.001$). Haloperidol by itself decreased locomotor activity compared with the saline control treatment ($p<0.001$). Administration of haloperidol also decreased locomotion in rats treated with tandospirone at both 0.05 mg/kg ($p<0.001$) and 5 mg/kg ($p<0.001$) (Fig. 3c).

There was significant interaction between tandospirone and haloperidol in MK-801-treated animals [F(2,53)=9.37, $p<0.001$]. Administration of haloperidol significantly decreased locomotor activity in MK-801-treated rats [F(1,53)=38.54, $p<0.001$]. Tukey's HSD post-hoc test showed that haloperidol decreased locomotor activity in tandospirone (0.05 mg/kg)/MK-801-treated rats ($p<0.001$), but not in tandospirone-treated rats (5 mg/kg). There was no main effect of tandospirone treatment [F(2,53)=1.97, NS] (Fig. 3c).

Discussion

Repeated administration of tandospirone at 0.05 or 5.0 mg/kg decreased PPI in rats that were not treated with MK-801 (Fig. 1a). To the best of our knowledge, the effect of tandospirone, a selective 5-HT1A partial agonist, on PPI has not been reported in either animals or humans. Stimulation of 5-HT1A receptors by 8-OH-DPAT (full agonist) or buspirone (partial agonist) decreases PPI (Bubenikova-Valesova et al. 2007b; van den Buuse and Gogos 2007). The effect of tandospirone at 5 mg/kg on PPI was prevented by the acute administration of WAY 100635, a selective 5-HT1A antagonist (Fornal et al. 1996), suggesting that tandospirone decreased PPI via selectively by acting on 5-HT1A receptors. Repeated administration of 5-HT1A receptor agonists desensitises 5-HT1A autoreceptors in the raphe nucleus, but not the postsynaptic receptors in projection areas (Hensler 2003). Therefore, it is possible that tandospirone elicited its effects on PPI via the postsynaptic 5-HT1A receptors, which were blocked by WAY 100635 (Fig. 2a). Interestingly, tandospirone at a dose of 0.05 mg/kg in repeated, but not in acute, administration (data not shown) induced PPI deficits, which were not affected by WAY 100635.

The level of the startle response indicates emotions and attention in rodents. A high startle response disrupts sensory and cognitive processing and is followed by an increase in the heart rate and the activation of other sympathetic systems (Yeomans et al. 2002). Tandospirone at a dose of 0.5 mg/kg increased the acoustic startle response, which was blocked by WAY 100635. An increase in the acoustic startle response was not evident at 5 mg/kg. We suggest that the increase in the startle response by tandospirone could influence the level of PPI.

Locomotor activity in the novel environment was decreased by tandospirone (5 mg/kg; Fig. 1c), which is in accordance with a report by an independent group of investigators (Miller et al. 1992) as well as with our previous findings using another 5-HT1A partial agonist buspirone (Ahlenius et al. 1993; Bubenikova-Valesova et al. 2007a; Haller et al. 2001). However, this is opposite to the response with the full agonist 8-OH-DPAT, which increased locomotor activity (Bubenikova-Valesova et al. 2007a), an effect that was suggested as being mediated by stimulation of the postsynaptic 5-HT1A receptors (Mignon and Wolf 2002). The inhibitory effect of buspirone on locomotion could be explained by its antagonist actions at D2 receptors (McMillen et al. 1983; McMillen and McDonald 1983), while tandospirone has little affinity for these receptors (Hamik et al. 1990).

The inhibitory effect of tandospirone on locomotion was potentiated by the acute administration of WAY 100635 (Fig. 2c). It is assumed that the effects of tandospirone or its metabolites on other neurotransmitter systems are responsible for the ability of this compound to decrease locomotor activity. Tandospirone and buspirone are metabolised to 1-(2-pyrimidinyl)-piperazine (1-PP) in rodents and humans