Sexual Medicine, 2024, **12**, qfae085
https://doi.org/10.1093/sexmed/qfae085
Original Research

Comparison of melanocortin-4 reptor and α-melanoside stimulated hormone levels in healthy female volunteers and female patients with and without sexual functional disorders related to the use of selective serotonin reaptake inhibitors

Simge N. Kurt Kaya, MD[1,*], Yasir Safak, MD[2], Seyda Ozdemir, MD[3]

[1]Department of Psychiatry, 29 Mayıs State Hospital, Ankara, 06105, Turkey
[2]Department of Psychiatry, Etlik City Hospital, Ankara, 06170, Turkey
[3]Department of Biochemistry, Etlik City Hospital, Ankara, 06170, Turkey
*Corresponding author: 29 Mayıs State Hospital, Ankara, 06105, Turkey. Email:smgkrt06@gmail.com

Abstract

Background: Sexual dysfunction (SD) due to Selective Serotonin Reuptake Inhibitors (SSRI) use is a common condition encountered by psychiatrists and its etiology has not been fully elucidated.
Aim: To determine the relationship between alpha Melanocyte Stimulating Hormone (α-MSH) and Melanocortin-4 receptor (MCR4) levels and sexual function levels of patients with and without SSRI related SD and control group and to examine whether α-MSH and MCR4 play a role in the etiology of SSRI related SD.
Methods: A total of 92 patients and 49 healthy volunteers who applied to psychiatry outpatient clinic were included in the study. Sociodemographic form, sexual history form, Structured Clinical Interview for DSM 5, Psychotropic Related Sexual Dysfunction-Turkish version (PreSexDQ-T), Arizona Sexual Experiences Scale, Beck Depression and Anxiety Inventory were used in the evaluation interview with the referred patients. Patient groups were formed according to whether there was SSRI related SD according to the sexual history and PreSexDQ-T scale.
Outcomes: The α-MSH and MCR4 levels were significantly lower in patients with SD due to SSRI use.
Results: α-MSH and MCR4 levels were lower in the SSRI related SD (SSRI-SD (+)) group than in the not experiencing SD with SSRIs (SSRI-SD (–)) and control groups. The mean α-MSH and MCR4 value of the control group was found to be significantly higher than the SSRI-SD (+) patient group, the mean MCR4 value of the control group was found to be significantly higher than the mean MCR4 value of the SSRI-SD (–) patient group. The mean MCR4 and a-MSH values of the SSRI-SD(+) group using SSRI with fluoxetine were significantly lower than the SSRI-SD (–) group using SSRI with fluoxetine.
Clinical implications: There is a role for α-MSH and MCR4 in SSRI related SD.
Strengths and limitations: Its strength is that it is the first human study in this field. Limitations include small sample size and unknown baseline levels of α-MSH and MCR4.
Conclusion: The fact that α-MSH and MCR4 play a role in the etiology of SD due to SSRI use in woman and that there was a significant difference between SSRI-SD (+) and SSRI-SD (–) groups when α-MSH and MCR4 levels were compared in fluoxetine users supports the hypothesis that serotonin may mediate SD via α-MSH and MCR4 through 5-hydroxytryptamine-2C (5-HT_{2C}) antagonism.

Keywords: antidepressants; sexual dsyfunction; melanocortin; A-melanocyte stimulated hormone.

Introduction

Sexual dysfunction (SD) refers to conditions that cause significant distress and/or difficulty in interpersonal relationships as a result of disruption in the psychophysiological processes that make up the sexual response cycle.[1] The sexual response cycle consists of phases including desire, arousal, plateau, orgasm and resolution.

There are both psychological and organic causes in the etiology of SD. SD due to psychotropic drug use are also quite common.[2,3] With the increasing use of selective serotonin reuptake inhibitors (SSRI) in the treatment of depression and anxiety disorders, SSRI related SD has become more common and recognized.[4] Controlled studies show that SD is associated with SSRI use at rates ranging from 40% to 70%.[5-7]

SSRI use can cause dsyfunction in all phases of the sexual response cycle.[8] Patient using SSRIs have reported experiencing different sexual side effects, including decreased sexual desire, delayed or absent orgasm, decreased vaginal lubrication, decreased genital sensation/anesthesia and erectile dysfunction. Serotonin (5-HT), noradrenaline (NA) and dopamine (DA) play a role not only in a person's mental state but also in the phases and functions of the sexual cycle. The increase in serotonin leads to a decrease in blood flow and arousal steps through NA via 5-HT_{1A}.[9]

Received: August 27, 2024. **Revised:** October 23, 2024. **Accepted:** December 7, 2024

SSRI-mediated stimulation of 5-HT_{2C} and 5-HT $_{2A}$ receptors in the spinal cord may suppress peripheral sympathetic and parasympathetic reflexes involved in sexual arousal, especially orgasm and ejaculation spinal reflexes, leading to SD.[10] Increased serotonin concentration in the mesolimbic pathway, resulting in DA inhibition by 5-HT_{2A} stimulation, may cause decrease of libido.[11] In some animal studies, when rats were injected with serotonin or given 5-HT_2 agonists, there was a significant reduction in sexual activity, and the reduction in the severity and frequency of drug-induced sexual side effects with 5-HT_2 antagonists such as mirtazapine supports the hypothesis that serotonin causes SD.[12]

Although the melanocortin system is well known for its effects on energy metabolism, appetite and weight changes, it is also involved in the reproductive system and sexual functions. The precursor of the melanocortin system family is proopiomelanocortin (POMC). The melanocortin family includes members such as adrenocorticotropic hormone (ACTH), α-, β-, γ- melanocortin stimulating hormone (MSH), g-protein coupled melanocortin receptors (MCR).[13,14] In recent studies, the occurrence of erection and ejaculation by injecting ACTH and α-MSH into the cerebroventricular area in animals has been interpreted in favor of a role for the melanocortin family of systems in sexual function.[15] There are also studies showing that sexual behavior is reduced when α-MSH is reduced, and that inhibition of the central activity of α-MSH and the use of MCR4 antagonists delay sexual behavior.[16,17]

5-HT interacted with POMC neurons in immunoreactive nerve terminals in the arcuate nuclei of the hypothalamus. The release of α-MSH, a POMC product, from the hypothalamus mediated by drugs acting through serotonin also proves this interaction.[18] In the light of these findings, it is thought that serotonin increases α-MSH release by affecting POMC in melanocortin pathways via 5-HT_{2C} and α-MSH shows agonist effect on MCR3-MCR4.[19]

In the publication by Bala et al. in 2017, which defined SD that persists after SSRI use as a new syndrome and reviewed the literature, it was emphasized that SSRIs that inhibit POMC outputs and MCR4 via 5-$HT_{2A\text{-}2C}$ may cause SD through this pathway.[19-21] Ortuno et al., 2021, in a study investigating the mechanism of weight gain of fluoxetine, it was shown that the amount of serotonin increased with 5-HT_{1A} blockade in mice given fluoxetine, decreased POMC and α-MSH levels by reducing 5-HT_{2C} signaling and gene expressions, and that the decrease in α-MSH level caused a decrease in MCR4 activation.[22]

Drug-induced SD is very common in practice, women discontinue their treatment for this reason, and clinicians have limited resources to manage these side effects. In the literature, how SSRIs cause SD in humans has not been fully elucidated, there are no human studies in this field. Since this mechanism is not fully known, appropriate treatment approaches cannot be established.[23]

Consequently, the primary objective of this study was to answer the following question: Is SSRI related SD in women associated with a-MSH and MCR4? There is no study in humans in this field, we thought that our study would contribute to the literature. The secondary aim was to analyze the relationship between a-MSH and MCR4 according to the active ingredients of the antidepressant used in female patients with SSRI related SD. As the final aim of the study, we aimed to elucidate the etiology of SSRI related SD in female patients.

Methods

We performed a case–control study. Patients who applied to the psychiatry outpatient clinic between January 2022 and January 2023 and were diagnosed with major depression and anxiety disorder according to DSM-5 diagnostic criteria were included. All participants provided written informed consent before enrollment, and the study was conducted in accordance with regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996)29 and approved by the local ethics committee (no. 128/01).

Patient group inclusion criteria were determined as being female and older than 18 years of age, not having entered menopause, using SSRIs regularly for at least 1 month and being willing to participate in the scales to be applied in the study, the evaluation and clinical interviews. The inclusion criteria for the healthy volunteer study were determined as follows: no impairment in sexual functions after psychiatric interview, Arizona Sexual Experience Scale (ASEX) scale scoring and sexual history form, not using medication that may cause impairment in sexual functions, female gender, being over 18 years of age and not having entered menopause and volunteering to participate. Mental conditions that prevent the interviews (dementia, active psychotic disorders, bipolar affective disorder during the episode period, momentary disability, etc.), physical limitations that prevent the interviews (visual-hearing problems that prevent the interview or filling out the form, etc.), physical illness that may cause SD, use of antipsychotics or mood stabilizers, use of drugs/substances known to cause SD (beta blockers, thiazide, kokain. Oral contraceptives, herbal product), having mental illness or severe relationship problems that may cause SD were determined as exclusion criteria for the patient and control group.

A total of 52 patients who had been on SSRIs for at least 1 month and had SSRI related sexual dysfunction (SSRI-SD (+)), 40 patients who did not have SSRI related sexual dysfunction (SSRI-SD (–)), and 49 healthy volunteers were included in the study. Participants were assessed according to inclusion and exclusion criteria by psychiatrists trained in clinical interviewing. Sociodemographic Data Form, Sexual History Form, Arizona Sexual Experiences Scale, Beck Anxiety and Depression Scale were completed by the participants. The Psychotropic-Related Sexual Dysfunction Scale -Turkisch version (PreSexDQ-T) was administered by the clinician.

Data collection tools

Socio-demographic Data Questionnaire: A detailed interview form prepared by our clinic, which is utilized to evaluate the age, gender, marital status, profession and educational background of patients.

Sexual History Form: This 28-item form contains questions pertaining to sexual relations, including intercourse, sexual drive, foreplay, frequency, duration, arousal and fulfillment.

ASEX: It is a scale developed by McGahuey et al. to assess the basic parts of sexual function (desire, arousal, penile erection/vaginal lubrication, orgasm and satisfaction.[24] It consists of five questions. The possible total score varies between 5 and 30. A higher total score on this scale indicates more SD. ASEX value of 19, a score of 5 on any question or a score of four on at least three questions indicates SD.

Psychotropic-Related Sexual Dysfunction Scale -Turkisch version (PreSexDQ-T): This is a scale specialized to screen for SD induced by medication use.[25] It is administered during

a face-to-face clinic interview. The questionnaire is made up of seven items. Items A and B are utilized at the beginning of the interview by the clinician to assess whether any changes have happened in sexual activity. For item A, the interviewer puts in the answer as either Yes or No. Likewise, for item B, the interviewer puts in whether the patient reported changes in sexual functions without being asked. Items A and B are utilized to assess whether any change in sexual activity exists and whether such change was spontaneously reported to the interviewer or not. Items A and B cannot be utilized to identify the level of SD. It is thus demonstrated that SSRI users can be divided as those with induced SD and those with no induced SD. The other five items assess the intensity or frequency of changes in sexual functions. Items 1 through 5 are utilized to evaluate decrease in libido, delayed orgasm/ejaculation, inability to orgasm/ejaculate, difficulty in obtaining and maintaining disruption in vaginal lubrication for females and tolerance of SD by the patient over scores ranging from 0 (less intensity or lower potential frequency) to 3 (more intensity or higher potential frequency). The final score of the questionnaire ranging between the lowest score of 0 (no SD) and the highest score of 15 (maximum SD) is obtained by adding up the scores given to items 1–5. If the final score of the questionnaire ranges between 1 and 5 and none of the items scored higher than 1, a "mild" SD is identified; likewise, with a final score ranging between 6 and 10 or any item scoring 2 and no item scoring 3 a "moderate", and a final score ranging between 11 and 15 or any item scoring 3 a "severe" SD is identified. In the presence of a total score of 0, SD is put in as "None".

Beck Anxiety Inventory (BAI): The BAI (Beck, Epstein et al., 1988) is a 21-item self-report instrument for assessing the severity of anxiety in psychiatric patients. Patients are asked to rate the severity of each symptom using a 4-point scale ranging from 0 to 3. A high total score indicates a high level of anxiety.[26]

Beck Depression Inventory (BDI): The original version of the BDI has 21 items and the total score can range from 0 to 63. It was developed to measure the risk of depression and the change in severity of depressive symptoms in adults. It is a 21-question scale that measures emotional, somatic, cognitive and motivational symptoms related to depression. A high total score indicates a high level of depressive symptoms.[27]

Statistical analysis

Since there is no previous human study in this field in the literature, a priori power analysis was performed for sample size estimation based on data from the study by Fehm et al.[28] examining the effects of melanocyte melanocortin on body weight. With a significance criterion of $\alpha = 0.05$ and power = 0.80, the minimum sample size needed for this effects size is 36 patients. Data obtained from participants were examined with IBM SPSS 26.0 (IBM Corp. Released 2015, IBM SPSS Statisticsfor Windows, Version 26.0. Armonk, NY: IBM Corp). The conformity of the data to normal distribution was examined by shapiro-wilktest. Square analysis was used to compare categorical variables. T-test was used between two groups for comparison of normally distributed data and Anova test was used for comparison of more than two groups. Mann–Whitney U test was used between two groups for comparison of non-normally distributed data and Kruskal-Walls test was used for comparison of more than two groups. Correlation analysis was used to analyze interrelated variables. Since the number of observations in the data set was low and the relationship between numerical variables and categorical variables was to be analyzed, Spearman Rho coefficient was used as the correlation coefficient. When the effect of some variables was wanted to be tested, it was used as a control variable and ANCOVA was used to analyze whether there was a difference between the groups in terms of measurement results. $P < .05$ was accepted for statistical significance level.

Biochemical analysis

Blood samples were collected from the participants by venipuncture at 08:00 in the morning after 12 h of fasting on a non-menstrual day, centrifuged at 1500 g for 10 min, placed in capped ependorf tubes and stored at –20°C. On the day of the ELISA study, the frozen sera were removed from –20°C, allowed to reach room temperature and then vortexed and studied in accordance with the kit package insert. (KITS: α-MSH: Human Alpha-MelanocyteStimulatingHormone(αMSH)ELISA Kit (Sunred-BiotechnologyShangai, China) 201-12-5500, MCR4: Human Melanocortin 4 Receptor (MC4R) ELISA Kit (SunredBiotech-nologyShangai, China) 201-12-4225).

Results

Descriptive statistics

The mean age of the SSRI-SD(+) patient group was 36.19 ± 7.53 years; the mean age of the SSRI-SD(–) patient group was 34.68 ± 6.51 years; and the mean age of the control group was 33.20 ± 5.12 years. There was no statistically significant difference between these three groups in terms of mean age ($P = .55$). (Table 1).

Average education duration and marital state are reported in Table 1.

No statistically significant difference was found in terms of the mean dose and duration of use of the drugs used by the participants.

Of the 92 female participants in the patient group, 60 (65.2%) were diagnosed with Unipolar Depression and 32 (34.8%) with Anxiety Disorders. Among the patients with anxiety disorders, 78.1% were diagnosed with Generalized Anxiety Disorder, 6.2% with Social Phobia and 15.7% with Panic Disorder.

In the 52-member SSRI-SD(+) group, 18 patients were using sertraline, 15 patients were using fluoxetine, 12 patients were using escitalopram and seven patients were using paroxetine. In the 40-member SSRI-SD(–) group, 19 patients were using sertraline, 9 patients were using fluoxetine, 10 patients were using escitalopram and two patients were using paroxetine.

Comparisons between groups

The mean α-MSH value of the SSRI-SD(+) patient group was 369.53 ± 787.30 ng/L; the mean α-MSH value of the SSRI-SD(–) patient group was 563.72 ± 848.83 ng/L; and the mean α-MSH value of the control group was 978.00 ± 1050.49 ng/L (Table 2).

There was a statistically significant difference between these three groups in terms of α-MSH value in at least one group

Table 1. Descriptive statistics for demographic and clinical characteristics.

Variables	Groups						*P*
	SSRI-SD (+)		SSRI- SD (–)		Control		
	N	%	N	%	N	%	
Sex							
Female	52	36.9	40	28.4	49	34.8	
Education							
Primary education	21	40.4	13	32.5	5	10.2	<.001*
High School	17	32.7	11	27.5	6	12.2	
University	14	26.9	16	40	38	77.6	
Average Education Duration (years)	11.00 ± 4.18		11.90 ± 4.29		14.53 ± 3.23		.00*
Marital Status							
Married	43	87.3	36	90	38	77.6	.298
Single	9	17.7	4	10	11	22.4	
Average Age (years)	36.19 ± 7.53		34.68 ± 6.51		33.20 ± 5.12		.055

Abbreviations: SD, Sexual dysfunction; SSRI, Serotonin Reuptake Inhibitors.

Table 2. Comparison of α-MSH and MCR4 levels between groups.

Variables	Groups			Test result
	SSRI-SD (+) (n = 52) Mean ± Std. Deviation	SSRI-SD(–) (n = 40) Mean ± Std. Deviation	Control (n = 49) Mean ± Std. Deviation	
α-MSH (ng/L)	369.53 ± 787.30 (a)	563.72 ± 848.83 (b)	978.00 ± 1050.49 (c)	$\chi^2 = 18.02$ $P < .001$* $c > a^m$
MCR4 (ng/L)	259.96 ± 414.38 (a)	390.69 ± 585.62 (b)	721.71 ± 601.09 (c)	$\chi^2 = 25.65$ $P < .001$* $c > a, c > b^m$

Abbreviations: α-MSH, alpha Melanocyte Stimulating Hormone; MCR4, Melanocortin-4 receptor; SD, Sexual dysfunction; SSRI, Serotonin Reuptake Inhibitors.

($P < .001$). According to the Dunnett C multiple comparison result, the mean α-MSH value of the control group was significantly higher than the mean α-MSH value of the SSRI-SD(+) patient group (Table 2).

The mean MCR4 value of the SSRI-SD(+) patient group was 259.96 ± 414.38 ng/L; the mean MCR4 value of the SSRI-SD(–) patient group was 390.69 ± 585.62 ng/L; and the mean MCR4 value of the control group was 721.71 ± 601.09 ng/L. There was a statistically significant difference between these three groups in terms of MCR4 values in at least one group ($P < .001$). According to Dunnett C multiple comparison result, the mean MCR4 value of the control group was significantly higher than the mean MCR4 value of the SSRI-SD (+) patient group. The mean MCR4 value of the control group was significantly higher than the mean MCR4 value of the SSRI-SD(–) patient group (Table 2).

The mean total ASEX score of the SSRI-SD (+) patient group was 20.08 ± 2.82; the mean total ASEX score of the SSRI-SD(–) patient group was 14.30 ± 2.72; and the mean total ASEX score of the control group was 11.96 ± 2.82. There was a statistically significant difference between these three groups in at least one group in terms of ASEX total scores ($P < .001$). According to Tukey's multiple comparison result, the mean total score of the ASEX of the SSRI-SD(+) patient group was significantly higher than the mean total score of the SSRI-SD(–) patient group, and the mean total score of the SSRI-SD(–) patient group was significantly higher than the mean total score of the ASEX of the control group (Table 3).

In all items of desire, arousal, vaginal lubrication, orgasm and satisfaction, the mean score of the SSRI-SD(+) patient group was significantly higher than the mean score of the SSRI-SD(–) patient group; the mean score of the SSRI-SD (–) patient group was significantly higher than the mean score of the control group (Table 3).

There was a statistically significant difference between these three groups in terms of BAI and BDI mean scores in at least one group ($P < .001$). According to the Dunnett C multiple comparison result, the mean BAI and BDI mean scores of the SSRI-SD(+) patient group were significantly higher than the mean scores of the control group. The mean BAI and BDI scores of the SSRI-SD(–) patient group were significantly higher than the mean score of the control group (Table 3).

The mean α-MSH value of the SSRI-SD(+) group using fluoxetine was 615.54 ± 1064.14 ng/L and the mean α-MSH value of the SSRI-SD(–) group was 1598.04 ± 1288.23 ng/L. There was a statistically significant difference between the patient groups using fluoxetine in terms of mean α-MSH value ($P = .049$). The mean α-MSH value of the SSRI-SD(–) group was higher than the mean α-MSH value of the SSRI-SD(+) group. The mean MCR4 value of the SSRI-SD (+) group using fluoxetine was 424.76 ± 526.83 ng/L and the mean MCR4 value of the SSRI-SD(–) group was 1037.43 ± 892.60 ng/L. There was a statistically significant difference in the mean MCR4 value between the groups of patients using ($P = .045$). The mean MCR4 value of the SSRI-SD(–) group was higher than the mean α-MSH value of the SSRI-SD(+) group (Table 4).

Table 3. Determination of difference between groups according to scales.

Variables	Groups			Test result
	SSRİ-SD(+) (n = 52) Mean ± Std. Deviation	SSRİ-SD(–) (n = 40) Mean ± Std. Deviation	Control (n = 49) Mean ± Std. Deviation	
ASEX Total Score	20.08 ± 2.82 (a)	14.30 ± 2.72 (b)	11.96 ± 2.82 (c)	F = 112.19 $P < .001^{**}$ $a > b > c^{n}$
ASEX-Desire	4.40 ± 0.95 (a)	3.20 ± 0.88 (b)	2.41 ± 0.95 (c)	$\chi^2 = 67.04$ $P < .001^{*}$ $a > b > c^{m}$
ASEX-Arousal	3.85 ± 0.97 (a)	2.63 ± 0.66 (b)	2.55 ± 0.73 (c)	$\chi^2 = 51.20$ $P < .001^{*}$ $a > b, a > c^{m}$
ASEX-Lubrication	3.87 ± 0.76 (a)	2.55 ± 0.87 (b)	2.43 ± 0.67 (c)	$\chi^2 = 63.08$ $P < .001^{*}$ $a > b, a > c^{m}$
ASEX-Orgasm	4.38 ± 0.77 (a)	3.28 ± 0.81 (b)	2.71 ± 0.76 (c)	$\chi^2 = 68.63$ $P < .001^{*}$ $a > b > c^{m}$
ASEX-Satisfaction	3.58 ± 1.03 (a)	2.65 ± 0.80 (b)	1.86 ± 0.81 (c)	$\chi^2 = 56.94$ $P < .001^{*}$ $a > b > c^{m}$
BDI	6.85 ± 2.29 (a)	6.30 ± 2.65 (b)	4.61 ± 2.75 (c)	$\chi^2 = 17.50$ $P < .001^{*}$ $a > c, b > c^{m}$
BAI	17.10 ± 11.14 (a)	15.08 ± 10.36 (b)	9.10 ± 6.73 (c)	$\chi^2 = 17.17$ $P < .001^{*}$ $a > c, b > c^{m}$

Abbreviations: ASES, Arizona Sexual Experience Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SD, Sexual dysfunction; SSRI, Serotonin Reuptake Inhibitors.

Table 4. Comparison of α-MSH and MCR4 levels between patient groups by active substance.

	Groups		
	SSRI-SD(+) Mean ± Std. Deviation	SSRI-SD(–) Mean ± Std. Deviation	Test result
Fluoxetine			
α-MSH	615.54 ± 1064.14	1598.04 ± 1288.23	4212/0.049*
MCR4	424.76 ± 526.83	1037.43 ± 892.60	7670/0.045*
Sertraline			
α-MSH	171.99 ± 83.85	310.34 ± 345.96	8762/0.108
MCR4	141.50 ± 206.48	249.73 ± 329.04	0.805/0.242
Paroxetine			
α-MSH	161.78 ± 79.21	116.93 ± 5.07	2609/0.471
MCR4	127.14 ± 53.17	138.75 ± 57.87	0.030/0.796
Escitalopram			
α-MSH	479.52 ± 1109.62	203.62 ± 117.94	2823/0.445
MCR4	309.13 ± 549.15	126.83 ± 96.64	2584/0.314

Abbreviations: α-MSH, alpha Melanocyte Stimulating Hormone; MCR4, Melanocortin-4 receptor; SD, Sexual dysfunction; SSRI, Serotonin Reuptake Inhibitors.

There is no statistically significant difference between α-MSH and MCR4 levels in patients taking sertraline, paroxetine and escitalopram in comparison between SSRI-SD (+) and SSRI-SD (–) groups (Table 4).

When the correlations were analyzed, it was observed that there were positive moderate correlations between α-MSH and MCR4 ($r = 0.447$; $P < .001$), negative moderate correlations between α-MSH and ASEX total score ($r = –0.589$; $P < .001$), and negative weak correlations between MCR4 and ASEX total score ($r = –0.310$; $P < .001$) for the SSRI-SD (+) patient group. There was no correlation between α-MSH and MCR4 with BAI, BDI and mean age.

Discussion

The reason for including only female patients in the study is that SSRIs are used in the treatment of psychogenic premature ejaculation and erectile dysfunction in men due to their anxiety-relieving effect. It is also consistent with the literature that the use of SSRIs may treat the existing disorder in male

patients instead of causing SD.[29] Since we aimed to elucidate the pathway of SSRIs causing SD in this study and since these drugs, which are known to be used in the treatment of SD in men, may have positive effects on male sexuality other than neutral effects, only female patients were selected considering the hypotheses of the study. SSRI-induced SD in male patients is a separate research topic.

Although there is no similar study conducted with only female patients, when the literature is examined, it is seen that the mean age in the studies in which SD was screened is similar to the mean age in our study.[30]

When the patient groups and the control group were compared in terms of α-MSH and MCR4 levels, the mean α-MSH and MCR4 values of the control group were significantly higher than the SSRI-SD (+) patient group, which means that people with drug-related SD were lower than people who did not have SD and did not use any antidepressant medication, which is consistent with our hypothesis that the pathway causing drug-related SDs occurs through α-MSH and MCR4. Our findings are consistent with animal studies investigating the relationship between α-MSH and MCR4 and SD.[15]

Although the mean α-MSH and MCR4 values of the SSRI-SD(–) patient group were significantly higher than the mean values of the SSRI-SD(+) patient group, the mean MCR4 value in the control group was significantly higher than the mean MCR4 value in the SSRI-SD(–) group, and the fact that there was no significant difference despite the higher mean value of α-MSH was interpreted in favor of SSRIs causing changes in sexual functioning, although not severe enough to diagnose SD.

By comparing the scale scores of individuals before drug use and after treatment or by observing drug use, it can be examined in further studies whether the fall will continue in the future and whether SD will occur. There is no human study evaluating the efficacy of α-MSH and MCR4 in SD. With this feature, this study is an exemplary study. It is a guide for future studies on this subject.

The finding that the mean scores of the SSRI-SD(+) patient group were significantly higher than the mean scores of the SSRI-SD(–) patient group in terms of desire, orgasm and satisfaction items of the ASEX, and the SSRI-SD(–) patient group were significantly higher than the mean scores of the control group in terms of desire, orgasm and satisfaction items of the ASEX is consistent with the literature that SSRIs cause impairment in areas such as desire, arousal, orgasm and lubrication.[31]

The finding of a significant difference between SSRI-SD (+) and SSRI-SD (–) patient groups in terms of mean α-MSH and MCR4 measurements only with fluoxetine is consistent with the studies in the literature suggesting that SD is induced by inhibiting α-MSH and MCR4 through 5-HT_{2C} antagonism. Fluoxetine has 5-HT_{2C} antagonism, which is not present in other SSRIs.[21] A significant difference may not have been found for sertraline, escitalopram and paroxetine due to the small sample size or although the basic mechanism for SSRIs is the same, it is known that they all have different binding on different receptors. For paroxetine, sexual side effects may be more likely due to anticholinergic mechanism, our results may indicate this. More reliable and generalisable results can be obtained with a larger number of samples.

Limitations

Although the sample group can be formed with higher numbers than the number found in the power analysis, studies with a larger number of sample groups may yield better results. Studies including male participants may yield more inclusive results as they will include larger populations. One limitation of our study was that the pre-drug α-MSH and MCR4 levels of the participants were not known. Blood samples were taken outside the menstrual cycle. No specific cycle time was determined for all patients, and the first and second blood samples were not planned to be taken at the same time of the cycle for the same patient. This situation was considered as a limitation. By eliminating these limitations, more generalisable and reliable results can be obtained.

Conclusion

This study supports the view that α-MSH and MCR4 are involved in the etiology of SSRI-induced SD in women. As the first human study in this field, it may benefit to obtain more generalisable results by eliminating limitations. It may be a preliminary study for the basis of new drug industry for drug-induced SD.

Acknowledgments

We express our gratitude to all the womans who participated in our study.

Author contributions

S.N.K.K.: Conceptualization. S.N.K.K, S.O.: Data curation. S.O.: Formalanalysis. S.N.K.K.: Investigation. Y.S.: Methodology. S.O.: Software. Y.S.: Supervision. Y.S.: Validation. S.N.K.K.: Visualization. S.N.K.K.: Writing–original draft. S.N.K.K., Y.S.: Writing–review and editing.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

The datasets are available from the corresponding author upon reasonable request.

Funding

The budget of the study was covered by the hospital with the decision of Dışkapı Training and Research Hospital Scientific Studies Support Board dated 10/2/2022 and numbered 83/08.

Ethics approval

Ethics committee approval for the study was obtained from Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee dated 10/01/2022 and numbered 128/01.

References

1. Srivastava R, Thakar R, Sultan A. Female sexual dysfunction in obstetrics and gynecology. *Obstet Gynecol Surv*. 2008;**63**(8):527–537. https://doi.org/10.1097/OGX.0b013e31817f13e3
2. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. The facts about sexual (Dys)function in schizophrenia: an overview of clinically relevant findings. *Schizophr Bull*. 2015;**41**(3):674–686. https://doi.org/10.1093/schbul/sbv001
3. Martínez-Giner G, Giménez-De Llano E, Romero-Rubio D. Sexual dysfunction in people treated with long-acting injectable antipsychotics in monotherapy or polypharmacy: a naturalistic study. *Int J Ment Health Nurs*. 2022;**31**(3):576–590. https://doi.org/10.1111/inm.12973
4. Steffens DC, Krishnan KRR, Helms MJ. Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. *Depress Anxiety*. 1997;**6**(1):10–18. https://doi.org/10.1002/(SICI)1520-6394(1997)6:1<10::AID-DA2>3.0.CO;2-9
5. Balon R. Sexual functioning with selective serotonin reuptake inhibitors. *Am J Psychiatry*. 1999;**156**(5):807–808. https://doi.org/10.1176/ajp.156.5.807
6. Bijlsma EY, Chan JS, Olivier B, *et al*. Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? *Pharmacol Biochem Behav*. 2014;**121**(6):88–101. https://doi.org/10.1016/j.pbb.2013.10.004
7. Montejo AL, Llorca G, Izquierdo J, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J Clin Psychiatry*. 2001;**62**(3):10–21.
8. La Torre A, Conca A, Duffy D, Giupponi G, Pompili M, Grözinger M. Sexual dysfunction related to psychotropic drugs: a critical review part II: antipsychotics. *Pharmacopsychiatry*. 2013;**46**(6):201–208. https://doi.org/10.1055/s-0033-1347177
9. Ahrold TK, Meston CM. Effects of SNS activation on SSRI-induced sexual side effects differ by SSRI. *J Sex Marital Ther*. 2009;**35**(4):311–319. https://doi.org/10.1080/00926230902851322
10. Yıldız A, Gönül AS, Tamam L. Mechanism of actions of antidepressants: beyond the receptors. *Bull Clin Psychopharmacol l*. 2002;**12**(3):194–200.
11. Pfaus JG. Pathways of sexual desire. *J Sex Med*. 2009;**6**(6):1506–1533. https://doi.org/10.1111/j.1743-6109.2009.01309.x
12. Labbate LA, Grimes JB, Hines A, Pollack MH. Bupropion treatment of serotonin reuptake antidepressant-associated sexual dysfunction. *Ann Clin Psychiatry*. 1997;**9**(4):241–245. https://doi.org/10.3109/10401239709147804
13. Wikberg JE, Mutulis F. Targeting melanocortin receptors: an approach to treat weight disorders and sexual dysfunction. *Nat Rev Drug Discov*. 2008;**7**(4):307–323. https://doi.org/10.1038/nrd2331
14. Gantz I, Fong TM. The melanocortin system. *Am J Physiol Endocrinol Metab*. 2003;**284**(3):E468–E474. https://doi.org/10.1152/ajpendo.00434.2002
15. Argiolas A, Melis MR, Murgia S, Schiöth HB. ACTH- and alpha-MSH-induced grooming, stretching, yawning and penile erection in male rats: site of action in the brain and role of melanocortin receptors. *Brain Res Bull*. 2000;**51**(5):425–431. https://doi.org/10.1016/S0361-9230(99)00270-1
16. Faulkner LD, Dowling AR, Stuart RC, Nillni EA, Hill JW. Reduced melanocortin production causes sexual dysfunction in male mice with POMC neuronal insulin and leptin insensitivity. *Endocrinology*. 2015;**156**(4):1372–1385. https://doi.org/10.1210/en.2014-1788
17. Caquineau C, Leng G, Guan XM, Jiang M, Van der Ploeg L, Douglas AJ. Effects of alpha-melanocyte-stimulating hormone on magnocellular oxytocin neurones and their activation at intromission in male rats. *J Neuroendocrinol*. 2006;**18**(9):685–691. https://doi.org/10.1111/j.1365-2826.2006.01465.x
18. Kiss I, Léránth C, Halász B. Serotoninergic endings on VIP-neurons in the suprachiasmatic nucleus and on ACTH-neurons in the arcuate nucleus of the rat hypothalamus. A combination of high resolution autoradiography and electron microscopic immunocytochemistry. *Neurosci Lett*. 1984;**44**(2):119–124. https://doi.org/10.1016/0304-3940(84)90068-5
19. Heisler LK, Cowley MA, Kishi T, *et al*. Central serotonin and melanocortin pathways regulating energy homeostasis. *Ann N Y Acad Sci*. 2003;**994**(1):169–174. https://doi.org/10.1111/j.1749-6632.2003.tb03177.x
20. Wright DE, Seroogy KB, Lundgren KH, Davis BM, Jennes L. Comparative localization of serotonin1A, 1C, and 2 receptor subtype mRNAs in rat brain. *J Comp Neurol*. 1995;**351**(3):357–373. https://doi.org/10.1002/cne.903510304
21. Bala A, Nguyen HMT, Hellstrom WJG. Post-SSRI sexual dysfunction: a literature review. *Sex Med Rev*. 2018;**6**(1):29–34. https://doi.org/10.1016/j.sxmr.2017.07.002
22. Ortuño MJ, Schneeberger M, Ilanges A, *et al*. Melanocortin 4 receptor stimulation prevents antidepressant-associated weight gain in mice caused by long-term fluoxetine exposure. *J Clin Invest*. 2021;**131**(24):1–14. https://doi.org/10.1172/JCI151976
23. Jing E, Straw-Wilson K. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: a narrative literature review. *Mental Health Clinician*. 2016;**6**(4):191–196. https://doi.org/10.9740/mhc.2016.07.191
24. McGahuey CA, Gelenberg AJ, Laukes CA, *et al*. The Arizona sexual experience scale (ASEX): reliability and validity. *J Sex Marital Ther*. 2000;**26**(1):25–40. https://doi.org/10.1080/009262300278623
25. Montejo AL, Garcia M, Espada M, *et al*. Psychometric characteristics of the psychotropic-related sexual dysfunction questionnaire. Spanish work group for the study of psychotropic-related sexual dysfunctions. *Actas Esp Psiquiatr*. 2000;**28**(3):141–150.
26. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;**56**(6):893–897. https://doi.org/10.1037/0022-006X.56.6.893
27. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;**4**(6):561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004
28. Fehm HL, Smolnik R, Kern W, McGregor GP, Bickel U, Born J. The melanocortin melanocyte-stimulating hormone/adrenocorticotropin(4-10) decreases body fat in humans. *J Clin Endocrinol Metab*. 2001;**86**(3):1144–1148. https://doi.org/10.1210/jcem.86.3.7298
29. Montejo-González AL, Llorca G, Izquierdo JA, *et al*. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther*. 1997;**23**(3):176–194. https://doi.org/10.1080/00926239708403923
30. Csoka AB, Bahrick A, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. *J Sex Med*. 2008;**5**(1):227–233. https://doi.org/10.1111/j.1743-6109.2007.00630.x
31. Keltner NL, McAfee KM, Taylor CL. Mechanisms and treatments of SSRI-induced sexual dysfunction. *Perspect Psychiatr Care*. 2002;**38**(3):111–116. https://doi.org/10.1111/j.1744-6163.2002.tb00665.x

Sexual Medicine, 2024, 12, qfae085
https://doi.org/10.1093/sexmed/qfae085
Original Research