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Chapter 4

Role for Pituitary Neuropeptides in Social Behavior Disturbances of Schizophrenia

Tomiki Sumiyoshi, Tadasu Matsuoka and Masayoshi Kurachi

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1. Introduction

Derangement of hormonal milieu has been associated with the pathophysiology of psychiatric illnesses, such as schizophrenia, mood disorders, and developmental disorders [1; 2; 3]. Among them, schizophrenia is a relatively common neuropsychiatric disorder, and has been associated with debilitating consequences if not treated properly [4; 5]. The illness is characterized by positive (e.g., delusions, hallucinations, bizarre thoughts) and negative (blunt affect, avolition, anhedonia, social withdrawal) symptoms, as well as deficits in various cognitive abilities, e.g. verbal memory, working memory, attention/vigilance, and information processing [4; 6; 7]. Minor impairments of social cognition are often observed during the premorbid stage of the disease [8].

The role for endocrinological dysregulation in the development of psychotic symptoms has been suggested by brain imaging studies. For example, a larger than normal volume of the pituitary gland has been reported in patients with first-episode schizophrenia [9] (Fig. 1). Further, these patients exhibit an increase in the pituitary volume overtime, unlike the case with normal volunteers, the degree of which is correlated with the change in positive symptoms [9]. These findings, representing mainly a morphological change of the anterior pituitary [9], are consistent with the concept of HPA axis hyperactivity in response to stress during psychotic experience [10].

Hormones secreted from the posterior portion of the pituitary gland, i.e. vasopressin and oxytocin, have also been a focus in schizophrenia research from the perspective of social behavior disturbances [2; 11; 12]. In this chapter, we provide an overview of preclinical and clinical evidence for contribution of the vasopressin and oxytocin systems in social behavior deficits of schizophrenia and related disorders, as well as their treatment. Related discussions on the role of these neuropeptides in the coping of stressors and psychiatric conditions are provided in other Chapters [3; 13].

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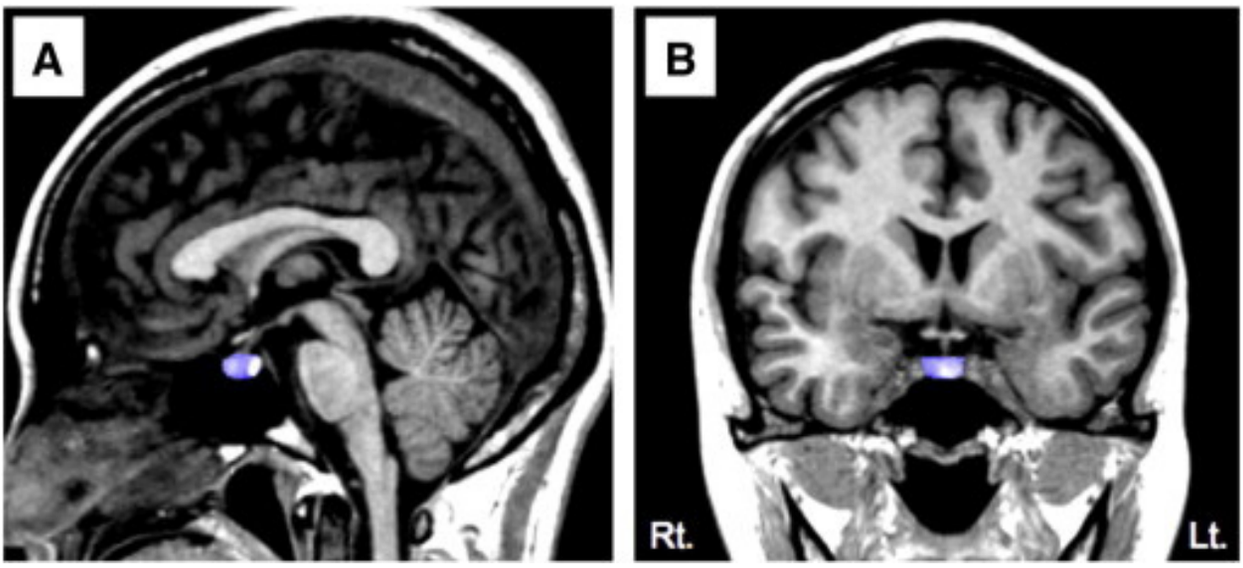


Figure 1. Sagittal (A) and coronal (B) views of the pituitary gland manually traced (in blue). The pituitary stalk was excluded from the tracings. (Takahashi T et al. *Prog Neuropsychopharmacol Biol Psychiatry* 35;177-83, 2011 (Permission obtained from Elsevier)

2. Vasopressin (arginine-vasopressin, AVP), oxytocin and behaviors

The two neuro-hormones are nona-peptides closely related each other, while their functions are sometimes in opposite directions, e.g. facial cognition and responses to stress [14]. Also, there is a suggestion that oxytocin is responsible for maternal behavior whereas male-typical social behavior is associated with AVP [2]. As a neuromodulator, AVP has been suggested to play a role in some of the cognitive abilities, including social memory, as well as emotionality (Fig 2). Neurotransmissions by AVP are mediated by three receptor subtypes, namely, V_{1A}, V_{1B}, and V_2 receptors, all of which are coupled to G-proteins [2]. Information about oxytocin is reviewed elsewhere in this Book [3]

Impaired social abilities have been particularly implicated in subjects with developmental disorders, such as autism. Thus, Fries et al (2005) [15] reported decreased urine levels of AVP and oxytocin, in children reared in orphanage settings compared to those in infants who received normal care-giving from their parents. Previously institutionalized children have been suggested to frequently experience problems in establishing social bonds and regulating social behavior [15]. Accordingly, infants who experienced early neglect showed lower basal levels of AVP than family-reared children [15]. These observations support the growing evidence for the role of the neuropeptidergic systems in social behaviors in mammals (e.g. [16; 17; 18]: see [19] for review).

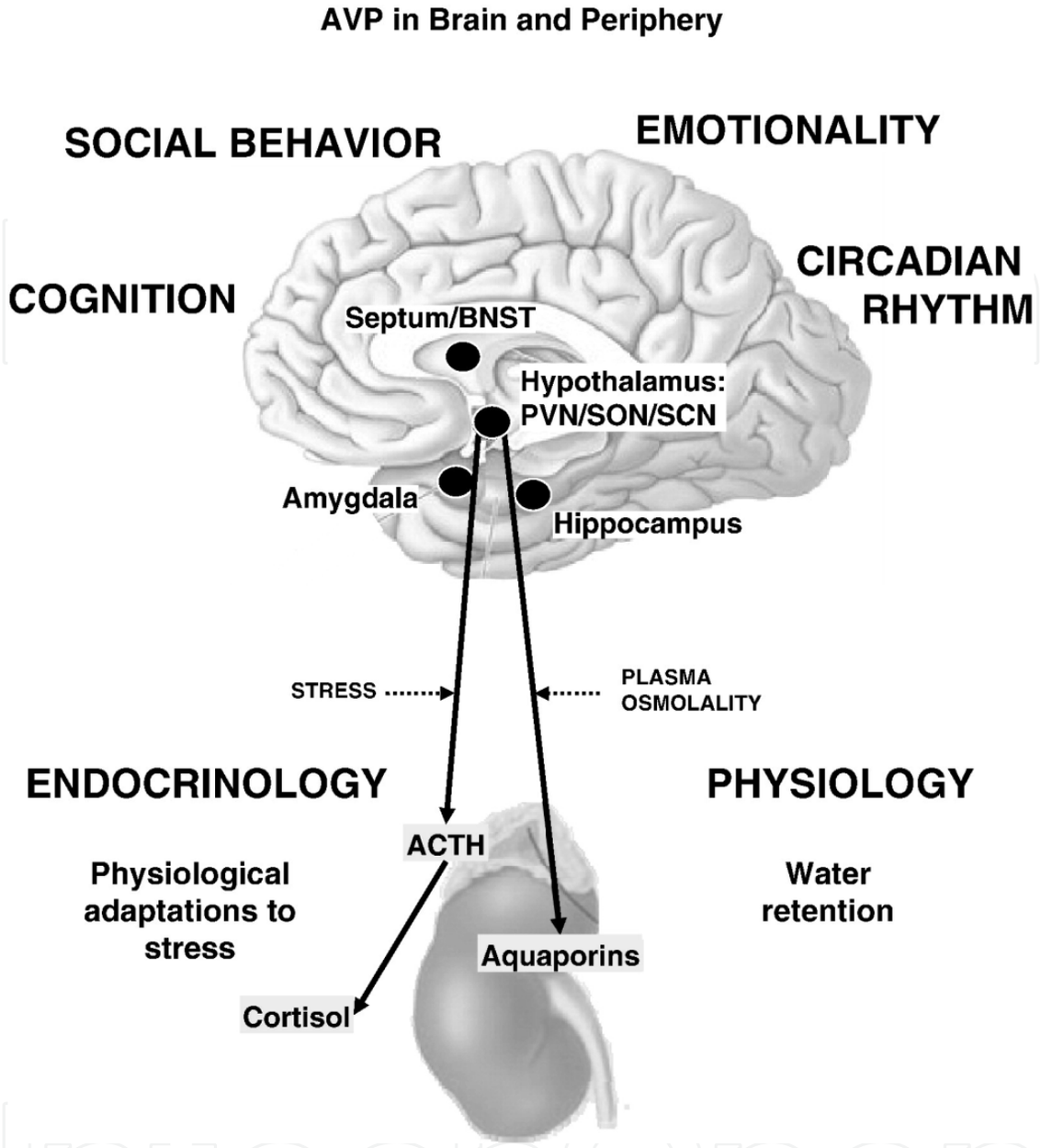


Figure 2. Arginine-vasopressin in the brain and periphery. Extracted from Frank E and Landgraf R. *Eur J Psychopharmacol* 583;226-42, 2008 (Permission obtained from Elsevier)

3. Sociality deficits in animal models of schizophrenia; Effect of neuropeptides

Social behaviors comprise various domains, such as social (learning) memory and social bonding [20; 21]. The intracerebroventricular administration of AVP has been shown to facilitate social memory, as measured by the social discrimination test (SDT), in rats [22; 23].

The neural substrates governing the ability of AVP to enhance sociality include the lateral septum (LS), bed nucleus of the stria terminalis, and medial amygdala [24]. Specifically, overexpression of the V_{1A} receptors in the LS enhanced SDT performance, an effect blocked

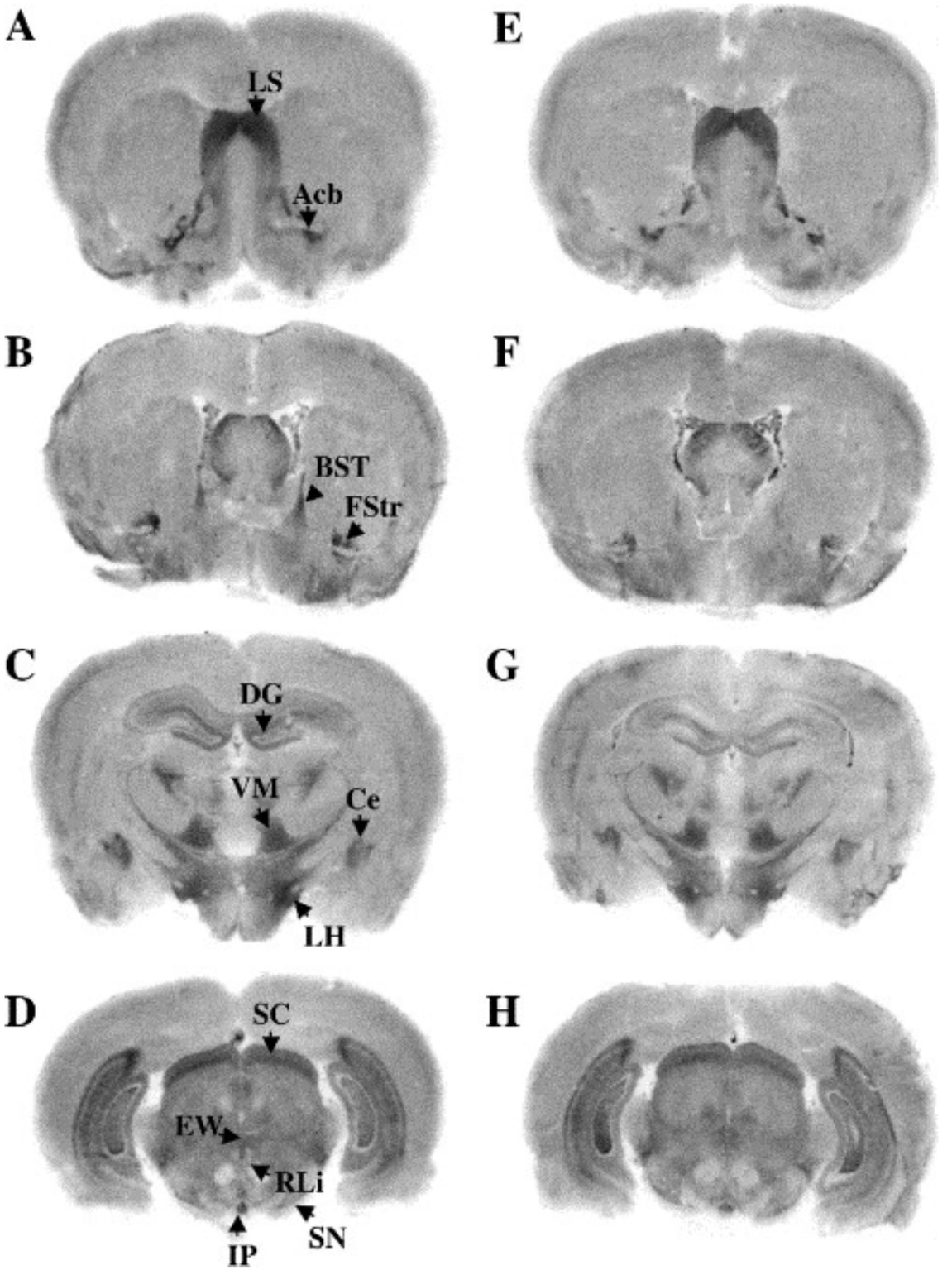


Figure 3. Autoradiographic localization of V1a receptor binding sites in coronal sections of the brain of the vehicle group (A–D) and PCP group (E–H) of rats with [^{125}I]-Linear AVP antagonist. Abbreviations: Acb, nucleus accumbens; FStr, fundus striati; LS, lateral septum; BST, bed nucleus of the stria terminalis; Ce, central amygdaloid nucleus; DG, dentate gyrus; VM, ventromedial thalamic nucleus; LH, lateral hypothalamic area; Rli, rostral linear raphe nucleus; SN, substantia nigra; IP, interpeduncular nucleus; SC, superior colliculus. Tanaka et al ., *Brain Res* 992; 239–245, 2003 (Permission obtained from Elsevier)

by application of a V_{1A} antagonist, but not oxytocin receptor antagonist [2]. By contrast, administration of oxytocin into the medial amygdala restored impaired social recognition in oxytocin knockout mice, while vasopressin was ineffective [25]. Overall, these observations are consistent with the contribution of V_1 receptors in the LS to the maintenance of long-term potentiation [26], which is crucial for learning and memory.

Experimental data from our laboratory also suggest a role for altered AVP transmissions in social interaction deficits. Thus, chronic administration of phencyclidine, an antagonist at N-methyl-D-aspartate (NMDA) receptors, impaired social interaction behavior, and reduced the density of V_{1A} receptors in several brain regions, including the LS in rats [18] (Figure 3). In a subsequent study, Matsuoka et al. (2008) [27] found decreased levels of mRNA encoding AVP in the amygdala, as measured by a microarray system and real-time quantitative PCR assay, in rats chronically treated with MK-801, a non-competitive antagonist at the NMDA receptor. These findings provide a basis for the ability of AVP or its analogues to ameliorate social interaction deficits in animal models of schizophrenia.

Accordingly, we reported that NC-1900, an AVP analogue and agonist at V1a receptors, ameliorates social interaction deficits in rats chronically treated with MK-801 [17] (Figure 4).

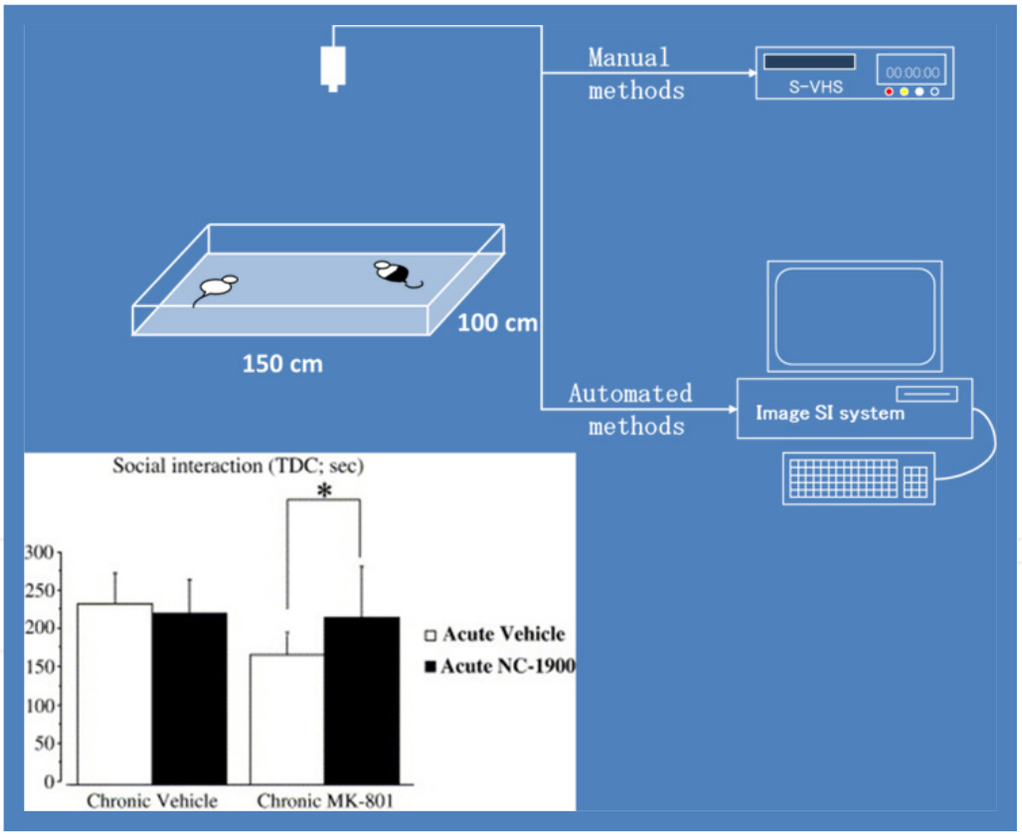


Figure 4. Measurement of social interaction behavior. A pair of rats (one dye-marked) are placed in an open arena, whose behavior, including "contact" (between-subject distance < 20 cm) is video-taped for manual viewing and/or automatically analyzed by a computer. (Inset)Total duration of contact (TDC) of rats during a 10-min observation period. Each bar represents mean ± SD of the time spent in social interaction (in seconds). *P < 0.05, chronic (MK-801, vehicle) × acute (NC-1900, vehicle) treatment interaction. Matsuoka et al. Brain Res 1053 (2005) 131-136. (Permission obtained from Elsevier).

This result from an animal model of schizophrenia is consistent with the observation, discussed above [18], that chronic administration of the NMDA antagonist phencyclidine reduces the density of V1a receptor binding sites in several brain regions, including the LS, in rats showing social interaction deficits. These findings from our laboratory are consistent with Bielsky et al [16] who reported that re-expressing of V1a receptors in the lateral septum of V1a receptor knockout mice exhibits complete recovery from impaired social recognition. Down-regulation of the AVP gene in the amygdala of MK-801-treated rats may provide a basis for the ability of AVP-analogues to ameliorate the behavioral disturbances by blockade of NMDA receptor [17]. Similar benefits regarding social behavior have been reported for oxytocin [3; 13; 28; 29; 30].

We conducted a further analysis of the change in the expression of RNAs encoding AVP and its receptor subtypes (V_{1A}, V_{1B}) in the amygdala of the model rat by means of qPCR (Table 1). As shown in Fig 5, expression of the AVP gene was significantly reduced by treatment with MK-801 (0.13 mg/day) for 14 days, while the same treatment did not affect the expressions of V_{1A}, and V_{1B} receptors. These results may help understand a mechanism by which impaired NMDA receptor-mediated transmissions, a putative pathophysiology of schizophrenia, disturbs social behaviors.

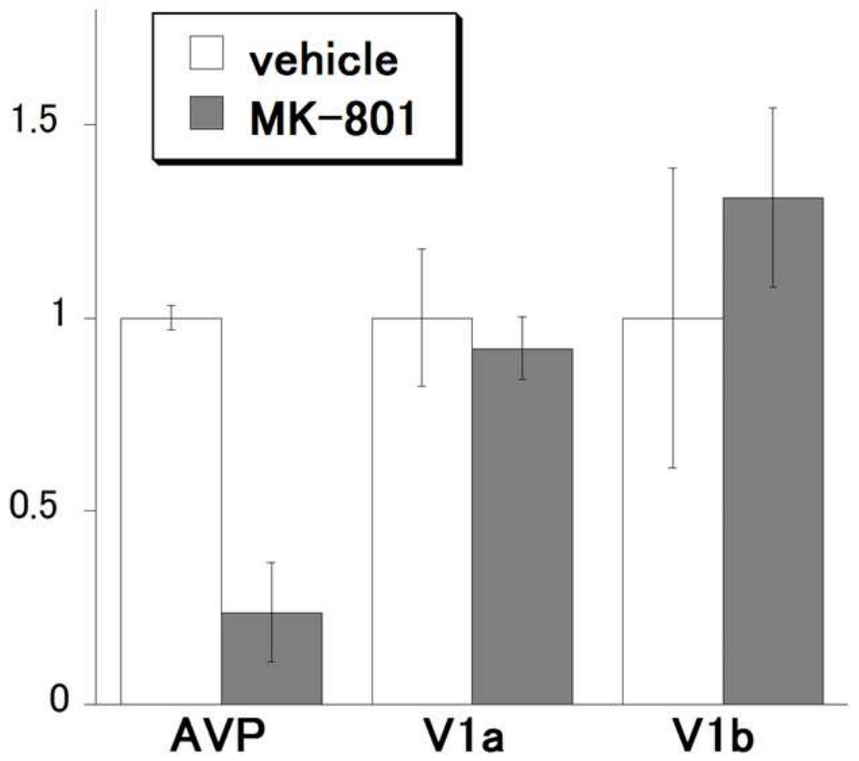


Figure 5. RNA quantification by means of real-time qPCR. Expression ratios for MK-801-treated rats vs. vehicle-treated animals are shown (n=5-6 for each group). Expression of the arginine-vasopressin (AVP) gene was significantly reduced by treatment with MK-801 (0.13 mg/day) for 14 days, (*$p<0.05$ by one-way ANOVA), while the same treatment did not affect the expressions of V1a and V1b receptors.Mx3000P (StrataGene) was used for pPCR with SYBER Premix Ex Taq (Takara Co. Ltd.). GAPDH was used as internal standard.

genes	forward	reverse	product size
GAPDH	tgaggaccaggttgtctcct	atgtaggccatgggtccac	162
AVP	acactacgctctctgcttg	cctcttgcctcctcttg	86
V1a	caaggatgactccgatagc	gatggatttggaagatttgg	112
V1b	ttctcagttgtgtggttcac	cctgtgcctttcagacttac	116

GAPDH, glyceraldehude-3-phosphate dehydrogenase.
AVP, arginine vasopressin. V1a, arginine vasopressin receptor 1a. V1b, vasopressin receptor 1b.

Table 1. Nucleotide sequences of RT-qPCR primers for target genes

4. Clinical implications

Efforts to enhance social ability are important from the perspective of adjusting patients to the community, thus improving functional outcome. Social ability disturbances in schizophrenia are thought to be partly attributable to negative symptoms and disturbances of cognitive function [4; 31; 32]. Although treatment with the first generation antipsychotic drugs, e.g. haloperidol, has been shown to ameliorate positive symptoms, only a limited number of agents, such as the second generation antipsychotics, or so-called "atypical antipsychotic drugs (AAPDs)", e.g. clozapine, melperone, risperidone, olanzapine, quetiapine, ziprasidone, and perospirone, with variable affinities for serotonin (5-HT) receptor subtypes, have been shown to be partially effective to treat negative symptoms and cognitive disturbances of schizophrenia [32; 33; 34; 35; 36] (see [4; 37] for review). Thus, more effective strategy to treat neurocognition, in addition to social abilities, is needed to enhance quality of life for patients.

In this context, the results from a recent study of the effect of augmentation therapy with oxytocin on cognitive function in patients with schizophrenia are noteworthy [38]. The investigators report a significant enhancement of verbal learning memory, a cognitive domain thought to largely influence the outcome, in subjects receiving daily intranasal oxytocin (twice daily) for 3 weeks. Further controlled study is warranted to confirm the cognition-boosting effect of neuropeptides in the treatment of schizophrenia.

As has been discussed, neuropeptides, e.g., vasopressin and oxytocin, have been suggested to be associated with the pathophysiology of schizophrenia. Accordingly, a whole-genome scan for schizophrenia in a large inbred Arab-Israeli pedigree has found a possible linkage on chromosome 20p13 [39] (Fig. 6). Importantly, this locus harbors four strong candidate genes for the illness, two of which are for oxytocin (*OXT*) and AVP (*AVP*) [39]. Further, examination of the association with gene expression in the brain identified genetic variants in the *OXT-AVP* cluster, and three of these variants were associated with schizophrenia [12]. These findings provide a strong proof for the contribution of these neuropeptides to the etiology of the illness.

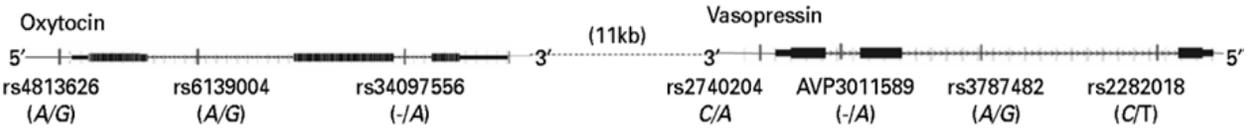


Figure 6. A scheme of the genes oxytocin and vasopressin on the chromosomal region 20p13 and the positions of the seven examined SNPs. Teltsh et al., *Int J Neuropsychopharmacol* 15;309-19, 2012 (Permission obtained from CINP).

5. Conclusions

Psychotropic drugs acting on 5-HT receptors, such as AAPDs and 5-HT$_{1A}$ agonists, have been shown to improve social behavior in animals [36; 40; 41]. These results are consistent with the concept that the AVP and 5-HT systems interact both neuroanatomically and neurochemically in the brain areas, e.g. anterior hypothalamus, as demonstrated in Fig. 7 [42]. Therefore, it is reasonable that further research into the neuropeptidergic system, in conjunction with other neurotransmitter/modulator systems, will facilitate the therapeutic strategy for social behavior deficits in patients with schizophrenia and related disorders.

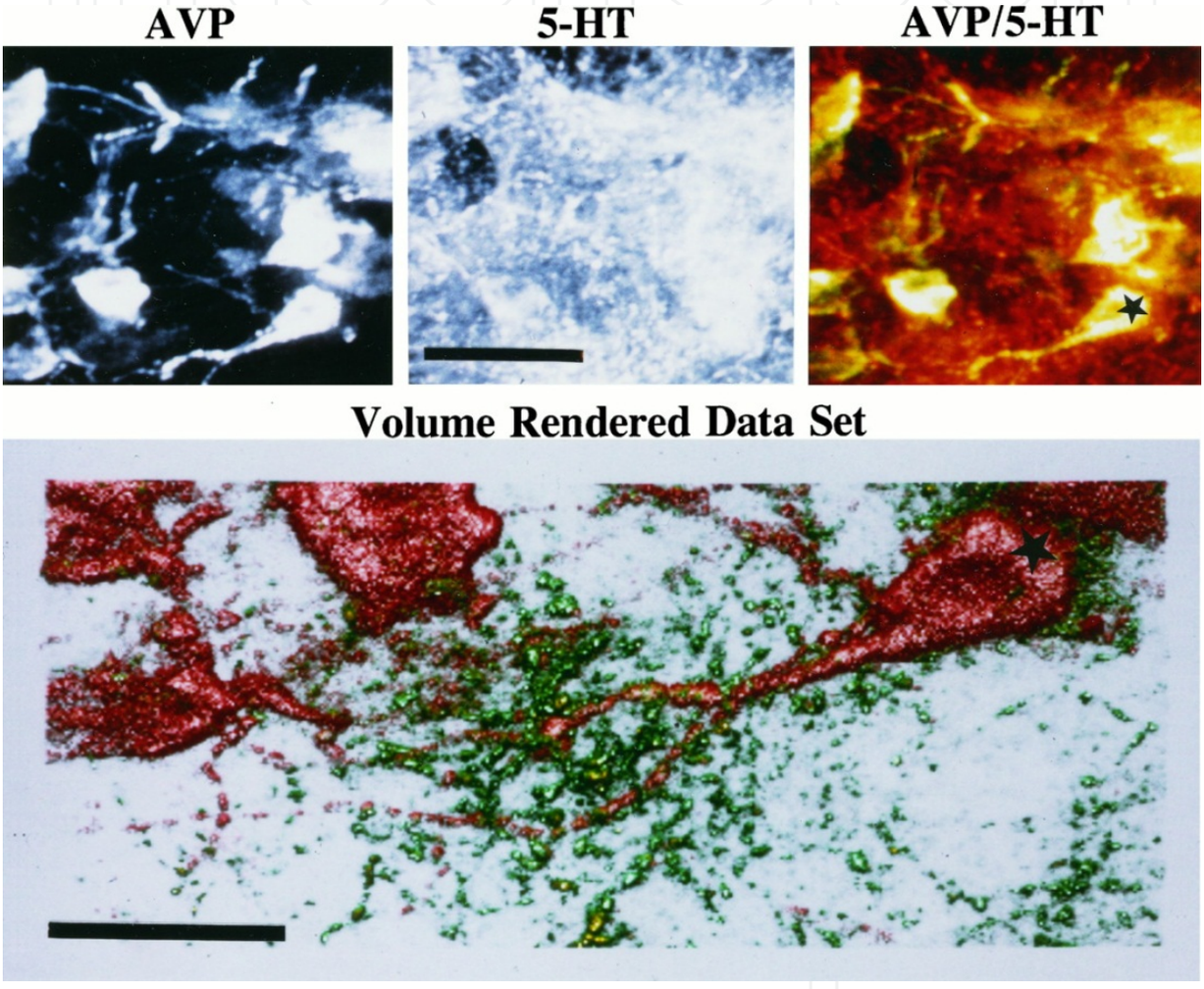


Figure 7. Photomicrographs of arginine vasopressin (AVP) and serotonin (5-HT), as revealed by double-labelling immunocytochemistry. Shown are AVP and 5-HT fluorescent immunoreactivity acquired through laser scanning confocal microscopy. The same single optical plane is shown for both neurochemical signals in the top black and white photographs. The combination of both digitized images is shown in color on the top right panel. The AVP is depicted in bright yellow and the 5-HT appears as a red/orange. A volume-rendered data set of serial optical sections through the AVP neuron denoted with the star is shown in the bottom color photograph. The green stippling is 5-HT varicosities and putative synapses clustered around the red-colored AVP neuron (denoted by the star). Scale bars: top, 50 μm; bottom, 30 μm. (Ferris C F et al. *J. Neurosci.* 1997;17:4331-43) (Permission obtained from the Society for Neuroscience)

Author details

Tomiki Sumiyoshi*, Tadasu Matsuoka and Masayoshi Kurachi
Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan

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* Corresponding Author

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