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Review article

Sexual orientation, neuropsychiatric disorders and the neurotransmitters involved

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ABSTRACT

According to the neuro-hormonal theory, sexual orientation in humans develops in the womb under the influence of sex hormones. In this article, we review the evidence from basic research on the possible role of neurotransmitters on influencing sexual orientation. We show that pharmacological or genetically induced changes in neurotransmitter systems during development might, by hormone-mediated structural and functional brain changes, result in alterations in sexual preference in animal models. We propose that in humans this mechanism may contribute to the relationship between non-heterosexual orientation and increased prevalence of neuropsychiatric disorders. Data to support this idea are reviewed. We suggest that altered neurotransmitter levels during development will increase the chance for both non-heterosexual differentiation of the brain and neuropsychiatric disorders. This possibility may have clinical implications, because medication given to a pregnant woman may, in this way, alter brain development of the fetus in a permanent way.

1. Introduction

Sexual orientation can be defined by the combination of sexual attraction, sexual behavior, and self-identification (Savin-Williams, 2009). Partners can be of the same sex (homosexual), opposite sex (heterosexual), or both sexes (bisexual) (Friedman et al., 1977). Explanations for the variation in sexual orientation have a very long history, from being an individual choice; being caused by the devil; being caused via factors in the social environment; to, currently, being caused by genetic, neurobiological and epigenetic influences (Ellis et al., 1987; Balthazart, 2020).

Nowadays, useful animal models have helped to frame questions and to propose hypotheses relevant to human sexual orientation, as described in Fig. 1. These tests, although imperfect, have been used to model certain aspects of human sexual orientation (Roselli, 2018). Experimental evidence in animal models and observations in humans suggest that sexual orientation is determined during early development as a result of the genetic background and factors which influence the interaction between sex hormones and the developing brain before birth (Bao and Swaab, 2010, 2011). In support of this idea, there is evidence from animal experiments indicating that modifying the sexual differentiation process of the developing brain, by altering the endocrine milieu, changes partner preference and the expression of specific patterns of sexual behavior, such as mounting behavior between males or the expression of typical female sexual behaviors in males, like lordosis (Bakker et al., 1993; Houtsmuller et al., 1994; Swaab et al., 1995; Henley et al., 2011; Olvera-Hernandez and Fernandez-Guasti, 2015; Olvera-Hernandez et al., 2019). Lordosis behavior is a female characteristic posture, displayed when the female is in behavioral estrous, that permits penile intromission. In males its display is inhibited by the organizational action of steroid hormones during development, known as the defeminization process (Tsukahara et al., 2014). Lordosis behavior is usually measured in males when the sexual differentiation process has been modified to have an idea of the degree of feminization.

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Non-manipulated males never show this behavior, even if castrated and administered with exogenous ovarian hormones in adulthood (Hennessey et al., 1986). However, if castration or other manipulations are made during the critical period of brain differentiation, males may express lordosis behavior in adulthood either spontaneously (Olvera-Hernandez and Fernandez-Guasti, 2015) or after the administration of estradiol plus progesterone (Olster and Blaustein, 1988).

In addition to the well-known role of hormones in establishing sex preference in laboratory animals, there is emerging new evidence showing that various pharmacological treatments may affect sex preference in animals. Such manipulations, applied either during development (from prenatal to pubertal periods) or in adulthood, reviewed below in detail, have been demonstrated to modify the sex preference or heterotypical sexual behavior in animals, though there are, as yet, no unequivocal results in humans. Interestingly, accumulating evidence indicates that non-heterosexual individuals have a higher risk for common neuropsychiatric disorders, such as mood, anxiety, and attention-deficit hyperactivity disorders (Sandfort et al., 2001; Frisell et al., 2010; Branstrom, 2017). Several causes have been proposed to explain this relationship, the minority stress theory being the most common and better supported (Sandfort et al., 2001; Frisell et al., 2010; Branstrom, 2017). However, other factors, such as personality traits (Park et al., 2016; Zaninotto et al., 2016), genetic traits (Zietsch et al., 2012), structural and functional cerebral characteristics and hormonal factors have also been mentioned as explanations (Hu et al., 2008; Abe et al., 2014; Abe, Rahman et al., 2018). There are reasons to believe that factors underlying the determination of sexual orientation may also take part in the development of neuropsychiatric disorders. Abnormalities in the regulation of neurotransmitters during development remain core components in the hypotheses on the neuronal foundation of behavioral and cognitive disorders (Iovino et al., 2018; Bernstein et al., 2019; Peedicayil, 2019). In the first part of this review, we show evidence that changes in neurotransmitters, during development or adulthood, may play a role in influencing sexual preference. In a second section, we detail the bidirectional relation between psychiatric problems and sexual orientation.

2. Methods

The main methodology consisted of a thoughtful analysis of published studies on the role of neurotransmitters in the development of both sexual orientation and neuropsychiatric disorders. Therefore, we considered the major original studies analyzing the effects of drugs on various neurotransmitter systems and their influence on sexual preference and neuropsychiatric disorders. A computerized research was performed to identify all relevant studies in PubMed from January 1970 up to September 2020. The following search terms were used: ("sexual orientation" [MeSH Terms] OR ("sexual" [All Fields] AND "orientation" [All Fields]) OR "sexual orientation" [All Fields]) OR ("sex preference" [MeSH Terms] OR ("sex" [All Fields] AND "preference" [All Fields]) OR "sex preference" [All Fields]) AND ("neurotransmitters" [MeSH Terms] OR "neurotransmitters" [All Fields]) OR ("serotonin" [MeSH Terms] OR "serotonin" [All Fields]) OR ("dopamine" [MeSH Terms] OR "dopamine" [All Fields]) OR ("GABA" [MeSH Terms] OR "GABA" [All Fields]) OR ("oxytocin" [MeSH Terms] OR "oxytocin" [All Fields]); ("neuropsychiatric disorders" [MeSH Terms] OR ("neuropsychiatric" [All Fields] AND "disorders" [All Fields]) OR "neuropsychiatric disorders" [All Fields] OR "neuropsychiatric diseases" [MeSH Terms] OR ("neuropsychiatric" [All Fields] AND "diseases" [All Fields]) OR "neuropsychiatric diseases [All Fields]) AND ("neurotransmitters" [MeSH Terms] OR "neurotransmitters" [All Fields]) OR ("serotonin" [MeSH Terms] OR "serotonin" [All Fields]) OR ("dopamine" [MeSH Terms] OR "dopamine" [All Fields]) OR ("GABA" [MeSH Terms] OR "GABA" [All Fields]) OR ("oxytocin" [MeSH Terms] OR "oxytocin" [All Fields]). Each of these search terms produced a list of significant studies that we selected in accordance with our aims and the interest for the reader.

3. Neurotransmitters and sexual preference

Sexual orientation (usually "orientation" is a human-centered concept) or sex preference (most commonly used in animals) involves several neurotransmitters. As aforementioned, the establishment of hetero-, homo- or bi-sexual behaviors may be influenced by several factors occurring during early development (Swaab et al., 2021). In addition, observations in animals and a few case reports in humans suggest that various drugs acting on the adult brain modulate sexual preference. It should be mentioned that most of the research in this field has studied males.

3.1. Biogenic amines

3.1.1. Serotonin

Serotonin is produced in the Raphe nuclei (Hornung, 2003) and plays an essential role in emotion, motivation and cognition (Murphy et al., 2004). In the 1960s and early 1970s, some data showed that p-chlorophenylalanine (pCPA), an irreversible inhibitor of tryptophan hydroxylase that depletes brain serotonin rather selectively, caused hypersexuality in cats, an effect that was putatively proposed to be mediated by the removal of an inhibitory serotoninergic mechanism

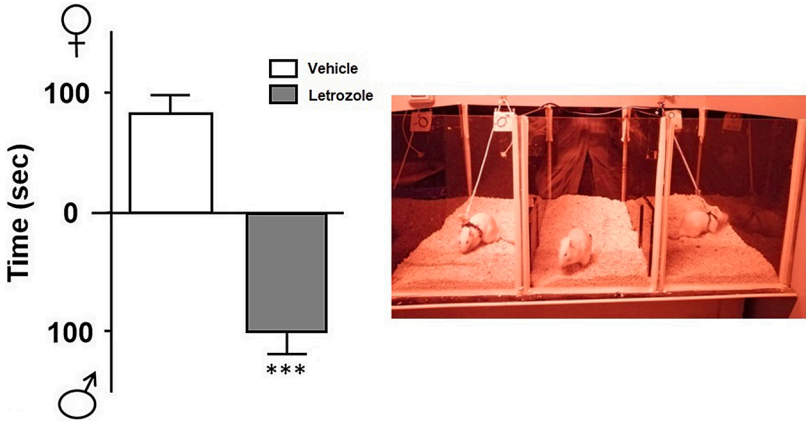

Fig. 1. Sexual preference tests measure the subject's motivation to approach and possibly interact with same-sex or opposite sex stimuli (Avitsur and Yirmiya, 1999). This three compartment test was described by Brand et al., (Brand et al., 1991). The left and right compartments contained stimulus animals (sexually receptive females and sexually experienced males) restrained with a harness but able to freely display sexual behavior (Olvera-Hernandez et al., 2015). During the test the experimental subject is placed in the middle compartment and allowed to interact with the stimulus. This test fulfils all criteria proposed by Vasey (Vasey, 2002) to consider it useful to measure sexual preference: (a) the subject should be able to simultaneously choose between a male and a female, (b) the two stimulus animals should ideally be sexually proceptive with regard to the subject, (c) the behaviors used to measure sexual partner preference are sexual, (d) at least in part, that the interaction must culminate in sexual behavior and (e) that the experimental subjects should have free will. Graph shows that control males (n = 20, unmanipulated or prenatally treated with vehicle) prefer to stay in the female's compartment, while those treated with letrozole (0.56 mg/kg, G10-G22, n = 36) stay most of the time in the male's area. ***p < 0.001, Student's *t*-test.

(Ferguson et al., 1970). Remarkably, pCPA administration to adult rats and rabbits produced more male-to-male mounting behavior (Sheard, 1969; Tagliamonte et al., 1969; Shillito, 1970; Sjoerdsma et al., 1970). A similar result was found after exposing animals to a tryptophan-free diet that decreased brain tryptophan, serotonin and its main metabolite, 5-hydroxy-indoleacetic acid (Fratta et al., 1977). Interestingly, male rats showed the typical female lordosis response after lesioning the mesencephalic dorsal raphe nucleus that contains most of the serotonergic somas of the neurons projecting into the forebrain (Kakeyama and Yamanouchi, 1992).

Consistently, a recent study reported that knockout (Tph2-/-) male mice to tryptophan hydroxylase 2 (Tph2) mounted other males with shorter latencies, higher frequencies and longer durations than control males (Tph2+/+) or heterozygous males (Tph2+/-). Tph2 is the rate-limiting enzyme in the production of brain serotonin (Walther et al., 2003). Moreover, the emission of ultrasound vocalizations that male mice produce when facing females was increased when these knockout males faced other males. Finally, males without serotonergic transmission lost preference for female pheromones over those of other males. All these findings suggest that an absent serotonergic transmission underlies a male–male sex-preference (Liu et al., 2011). This suggestion was further supported by the observation that injection of the serotonin (5-HT) precursor, 5-hydroxytryptophan (5-HTP) reduced male-male mounting of Tph2-/- mice while they regained heterosexual preference (Liu et al., 2011). Finally, male mice treated with pCPA behaved as Tph2-/- animals, i.e., they lacked female-preference. Nevertheless, these results were not replicated by another group (Angoa-Perez et al., 2015). They concluded that brain 5-HT signaling did not determine sexual preference in male mice and that the sex partner preference change observed in Liu's study may be explained by the serious adverse effects of the pharmacological agents that are non-selective for the 5-HT neuronal system. More studies are needed to specify the potential roles of 5-HT precisely.

Regarding females, a similar study in LIM homeobox transcription factor 1-beta (Lmx1b) and Tph2 knockout female mice, which also lacked central serotonergic transmission from embryogenesis to adulthood, revealed that they prefer female over male genital odors when given a choice, and displayed increased female-female mounting when presented either with a male or a female target (Zhang et al., 2013). Note that Lmx1b is a continuously expressed, terminal selector-type factor in serotonin neurons that plays an initial role in the induction of serotonin synthesis and transport (Hobert, 2008).

Another observation in favor of the involvement of the serotonergic system in the development of same-sex preference, and suggesting a possible link between sexual preference and emotional alterations due to similar underlying mechanisms, is the result of the effect of fluoxetine. Fluoxetine, one of the selective serotonin reuptake inhibitors (SSRIs), and the most commonly prescribed antidepressant worldwide, when given acutely, produces a challenge to the serotonergic system (Benfield et al., 1986). In rats, we found that in males with same sex preference - induced by prenatal treatment with letrozole, an aromatase inhibitor - the acute treatment with a single dose of fluoxetine (10 mg/kg, 3.5 h before the elevated plus maze test, EPM) produced no effect. Conversely, in male animals that were not treated prenatally, and had a female sex preference, a clear anxiogenic-like effect of fluoxetine was observed, manifested as spending less time in and showing lower number of entries to the open arms of the EPM (Garcia-Cardenas et al., 2015). These results showed that the effect of this SSRI might vary depending on the sex preference of the subjects. In agreement, in humans, a single oral administration of fluoxetine resulted in metabolic differences in some brain regions between homosexual (Kinsey 6 subjects) and heterosexual men. Thus, using positron emission tomography (PET) it was found that after fluoxetine in homosexual men the hypothalamus and the cingulate cortex showed a smaller activation in comparison with that of heterosexuals, while in the prefrontal cortex of homosexual men there was a higher metabolism than in heterosexuals. Conversely, in heterosexual men, the fluoxetine challenge produced a higher activation of the anterior cingulate cortex and the hippocampus than in homosexuals, while the parietal cortex remained without change (Kinnunen et al., 2004). These data might reflect underlying neurochemical differences related to sexual orientation that account for a divergent fluoxetine effect between homosexual and heterosexual men. These results, taken together, indicate that fluoxetine might produce a divergent action in relation to sexual preference, both in rats and humans, and further supports the idea that serotonin might be involved in sexual preference.

However, in rats and humans, the chronic administration of the SSRIs fluoxetine or citalopram, during several days or weeks, has failed to produce differential effects according to the sexual preference/orientation (Wainberg et al., 2006; Hernandez and Fernandez-Guasti, 2018).

3.1.2. Dopamine

Dopamine is produced in the ventral tegmental area (VTA), substantia nigra (SN) and hypothalamus (Slaney et al., 2013). Dopamine can, via different receptors, regulate many aspects of brain development and behavior (Klein et al., 2019). Some experiments suggest that changes in the dopaminergic system can alter sexual preference in both animals and humans. Dopamine may participate in the formation of sexual preference during development in *Drosophila melanogaster*. Using genetic and pharmacological approaches to decrease dopamine levels proved to enhance the attractiveness of males for other males (Liu et al., 2009). Moreover, the mutation of the dopamine D_1-like receptor (DopR) resulted in male-to-male courtship behavior, and expression of functional DopR successfully reverted this mutant phenotype (Chen et al., 2012).

An interesting series of studies (Gotz et al., 1989; Tonjes et al., 1989; Gotz et al., 1991) showed that lisuride (a dopamine agonist), administered to early postnatal (day 2–12) or peripubertal (day 26–40) female rats, increased male-typical behaviors and induced a partial conversion of sexual preference to the heterotypical male direction. In neonatally castrated or prenatally stressed males, which exhibit female sexual behavior and sex preference for other males (Hernandez et al., 2020), treatment with lisuride resulted in a temporary normalization of sexual preference, in the homotypical male direction, limited to the duration of treatment (Gotz et al., 1991). These findings confirm that neurotransmitters act directly as brain organizers during the differentiation and peripubertal maturation periods.

The effect of the dopamine D2-type receptor agonist, quinpirole, was examined on learning-conditioned sexual preference in rats. Males, but not females, learn to exhibit same-sex preference after cohabitation under the effects of quinpirole (Cibrian-Llanderal et al., 2012). Moreover, this effect was facilitated by co-administration of oxytocin (Triana-Del Rio et al., 2015).

In humans there is a single study relating the influence of dopamine on sexual orientation. Aripiprazole is an atypical antipsychotic drug with partial agonistic activity at dopamine D2 and D3 receptors, partial agonist to 5-HT1A and antagonist to 5-HT2A receptors (Frankel and Schwartz, 2017). A case report revealed a 28-year-old male patient diagnosed with schizoid personality disorder, who after being treated with aripiprazole, switched from an exclusive heterosexual with poor sexual activity to hypersexuality with homosexual behavior (Mete et al., 2016). Interestingly, two weeks after discontinuing aripiprazole, he ceased his compulsive sexual behavior and reported a return to heterosexual orientation.

3.2. Amino acid neurotransmitters (GABA)

The medial preoptic area (MPOA) of the rat hypothalamus contains the sexually dimorphic nucleus (SDN), which is 2–7 times larger in males than in females (Gorski et al., 1980). The difference in this brain area is related to the early endocrine milieu, thus perinatal androgen produced by the testes in males induces a larger SDN-POA (Dohler et al.,

1982; Davis et al., 1995). The SDN of the MPOA appears to be related to sexual preference, because its lesion in male ferrets or rats changes partner preference (Van De Poll and Van Dis, 1979; Paredes and Baum, 1995; Kindon et al., 1996; Paredes et al., 1998). Interestingly, the volume of the MPOA is smaller in rats that were prenatally treated with the steroidal aromatase inhibitor, 1,4,6-androstatriene-317-dione (ATD), and that had a diminished sexual preference for females (Houtsmuller et al., 1994). Remarkably, in 1996, Bakker et al., using c-Fos as a marker of neuronal activation, showed that in male rats that had same-sex preference, there was an activation in the MPOA when these males were exposed to olfactory cues of sexually active males (Bakker et al., 1996). Such activation did not occur in control males with female preference, and was similar to that found in females that prefer males. As a reminder, the c-Fos technique indicates neuronal activity and permits the analysis of many brain regions in the same brain due to the fact that neurons respond to stimulation by rapidly and transiently transcribing and subsequently translating the c-fos gene (Phillips-Farfan and Fernandez-Guasti, 2009; Hoffman, 2020).

The development of the SDN-MPOA may be affected by the GABAergic system. Male rats treated perinatally with muscimol, a $GABA_A$ receptor agonist, showed significantly smaller SDN-MPOA volumes compared to controls (Bach et al., 1992). Treating male rats perinatally with picrotoxin, a $GABA_A$ receptor antagonist, caused a decrease in the number of mounts in adulthood. In addition, when these males were castrated and pretreated with exogenous estrogen showed more lordosis behavior and acceptance of mounting in the presence of other sexually experienced males. Other studies showed that perinatal picrotoxin treatment reduced the lordosis response and mounts toward same-sex animals in sexually inexperienced male rats (Teodorov et al., 2002) and more heterosexual behavior in male offspring, in parameters such as mounting and intromission latencies to receptive female rats (Teodorov et al., 2006). The GABAergic system might thus be involved, to some extent, in the formation of sexual preference.

3.3. Peptides (oxytocin)

3.3.1. Oxytocin

No direct evidence was found in the literature on the role of oxytocin on the modulation or establishment of sexual preference, although there is some circumstantial evidence. Bisphenol A was used to manufacture polycarbonate plastics and epoxy resin (Michalowicz, 2014). This compound may inhibit social interactions with the opposite sex, but demonstrated improved socio-sexual exploration and a low-intensity mounting with the same sex in rats (Gao et al., 2020). This effect could be mediated via the oxytocinergic system, because bisphenol A, in addition to disrupting the steroid receptor expression (particularly estrogen) in the developing brain (MacKay and Abizaid, 2018), produces oxytocinergic alterations, such as disruption of oxytocin expression in the male and female hippocampus and hypothalamus (Arambula et al., 2016), as well as oxytocin receptor alterations in the amygdala (Arambula et al., 2018), the bed nucleus of the stria terminalis, the ventromedial hypothalamus and the paraventricular nucleus (Witchey et al., 2019).

Most of the animal studies on the effects of oxytocin on sexual preference and behavior have been performed on female meadow voles, who form social preferences for familiar same-sex peers under short, winter-like day lengths (Meek and Lee, 1993). This provides a means of studying affiliation beyond the context of reproductive pair bonding in the laboratory. Infusing oxytocin into the lateral septum of female meadow voles prevented cohabitation with a female partner immediately prior to cohabitation with a social male partner. Co-administration of oxytocin with a specific oxytocin receptor antagonist did not reverse the effect, but co-administration of oxytocin with a specific vasopressin 1a receptor (V1aR) antagonist did, indicating that oxytocin in the lateral septum acts probably through V1aR to decrease female same-sex partner preference (Anacker et al., 2016). Researchers also found that oxytocin receptor activation in the ventral tegmental area (VTA) is necessary for same-sex social interaction in both male and female Syrian hamsters. A highly selective oxytocin receptor antagonist could significantly decrease the time spent with same-sex partners (Borland et al., 2019). In rats, as aforementioned, learning-conditioned same-sex preference could develop by administering quinpirole or oxytocin either alone or together (Triana-Del Rio et al., 2015). Though the number of oxytocin neurons in the paraventricular nucleus did not seem to be related to sexual orientation (Purba et al., 1993), researchers did find oxytocin had stronger impact on social face processing in homosexual men than in heterosexual men. This indicates that oxytocin may play a different role in the regulation of social interactions according to sexual orientation (Thienel et al., 2014).

As we can see, the studies exposing a relationship between neurotransmitter changes and sexual preference are mostly focused on experimental animals. In humans, the evidence is scarce and far from conclusive.

4. Neuropsychiatric disorders vary in prevalence according to sexual orientation

Consistently, several studies using large samples have shown that non-heterosexual people have a higher risk for developing neuropsychiatric disorders than do heterosexuals. Thus, individuals who identified themselves as lesbian, gay or bisexual were reported to have 1.5–2.6 times higher risks for depression and anxiety than heterosexuals (King et al., 2008; Petterson et al., 2017). A much larger review (Bostwick et al., 2010) in the United States also revealed that lesbian, gay, or bisexual subjects were associated with high odds of any mood or anxiety disorder for both sexes. Furthermore, bisexual behavior conferred the highest odds of any mood or anxiety disorder for both males and females (Semlyen et al., 2016; Scott et al., 2017).

From another perspective, studies have found that psychiatric patients have a higher prevalence of homosexuality or bisexuality. Consistent with these findings, suicidal thoughts and attempts are significantly more prevalent among non-heterosexuals (Fergusson et al., 2005; Conron et al., 2010). In addition, eating disorder in male patients displayed marked differences in terms of sexual orientation. It is reported that 42 % of the male bulimic patients were either homosexual or bisexual, and 58 % of all male anorexic patients were identified as asexual (Carlat et al., 1997). Men with borderline personality disorder are more frequently homosexual (22 %) than are men in the general population (Neeleman, 2007). For autism spectrum disorder, the number of young male patients with a bisexual orientation appeared to be high (13 %) (Hellemans et al., 2007). Furthermore, negative health consequences such as substance abuse (Marshal et al., 2008; Bos et al., 2015), or body image dissatisfaction are also more prevalent in non-heterosexuals (Siever, 1994). Prevalence of schizophrenia and psychotic illness or episode were higher in gay men and men who were not sure of their sexual orientation (Bolton and Sareen, 2011).

This higher prevalence of psychiatric alterations in non-heterosexuals is, at least partly, due to social stigma and victimization throughout their life span, including early childhood (Hatzenbuehler and Pachankis, 2016). However, other studies propose that, in addition to discrimination, other causal factors may contribute to the higher prevalence of psychiatric disorders in this population. For example, one study showed that genetic factors accounted for a majority (60 %) of the correlation between sexual orientation and depression (Zietsch et al., 2012); another one revealed that in the Netherlands, where the general attitude towards non-heterosexual orientation is quite positive, there was a higher prevalence of psychiatric disorders among homosexuals, compared with their heterosexual counterparts (Sandfort et al., 2001).

The use of animal models could be particularly useful to explore whether behavioral cues interpreted as features of anxiety or depression are more frequently displayed by animals that have same-sex preference spontaneously or induced by endocrine manipulations during early

development. Such studies have the advantage of dismissing stigma, discrimination, homophobia or incessant bullying that many sexual minorities experience, leaving exposed possible biological factors underlying this high association. However, animal studies have the caveat of using models that cannot mimic all the characteristics; for example, several features of schizophrenia, depressed mood and homosexuality are exclusively human-centered concepts.

Using rats as experimental subjects, we found higher values of experimental anxiety in the EPM and despair in the forced swim test in the males with same-sex preference (Garcia-Cardenas et al., 2015; Hernandez and Fernandez-Guasti, 2018). It could be argued that the higher levels of anxiety and despair in these rats were due to the prenatal treatment with the aromatase inhibitor used to change partner-preference, rather than to the expression of this preference. Contrary to this idea, we found a similar increase in anxiety-like behaviors in spontaneously male-oriented male rats, supporting the idea that such an increase was associated with sex preference (Garcia--Cardenas et al., 2015). The mechanisms underlying this interesting association are unknown, but some speculations have been made.

Brain aromatase activity is primarily found in sexually dimorphic areas including the amygdala, the bed nucleus of the stria terminalis, the paraventricular preoptic area and the ventromedial hypothalamic nucleus (Roselli and Resko, 1993). Interestingly, these areas, in addition to their role in determining sex preference (Houtsmuller et al., 1994; Paredes and Baum, 1995; Paredes et al., 1998; Kondo and Sachs, 2002; Coria-Avila et al., 2018), participate in the control of various emotional processes, including anxiety and depression. Researchers found that aromatase knockout (ArKO) female mice exhibited a depressive-like profile in the forced swim test, because they displayed fewer active behaviors and increased passive behaviors, such as immobility (reflecting despair) (Dalla et al., 2004); similar results were not observed in male mice (Dalla et al., 2005). (Silveira et al., 1993) showed that after exposing male animals to the EPM, there was an increased c-Fos expression in brain areas rich in aromatase, such as the amygdala, the bed nucleus of the stria terminalis, and the anterior hypothalamic area, among others. Additional evidence in favor of this association was raised by the group of Adekunbi and co-workers in 2018. They hypothesized that the medial amygdala kisspeptin neurons could be involved in regulating attraction towards opposite-sex conspecifics as well as experimental anxiety. They found that after selectively stimulating these neurons, there was an increase in the time spent by male mice investigating estrous females. Additionally, there was an increase in the duration of social interaction, accompanied by a reduction in experimental anxiety when tested in the EPM. The authors concluded that activation of medial amygdala kisspeptin neurons enhanced the males' sexual partner preference for females, and decreased anxiety-like behaviors (Adekunbi et al., 2018). Remarkably, this association has also been demonstrated in clinics: the enhancement of limbic brain activity by kisspeptin in men viewing sexual images correlates with the attenuation of negative mood and reduced sexual aversion (Comninos et al., 2017). These associations, however, have still to be explored in subjects with same-sex preference.

Furthermore, specific disrupts in certain neurotransmitter systems, particularly the serotonergic (see above), may underlie same-sex preference and higher levels of despair (Hernandez and Fernandez-Guasti, 2018). Thus, in the forced swim test, we found an increased immobility accompanied by reduced swimming in male rats having same-sex preference. This result suggests involvement of the serotonergic system, because treatment with drugs that increase serotonergic transmission also reduce immobility and increase swimming (Nagayama et al., 1991; Detke et al., 1995; Lucki, 1998; Blier and de Montigny, 1999). These data suggest interactions among sex preference; changes in the serotonergic system; and levels of despair, which is one of the main features of depression. Overall, these data reinforce the idea that same-sex preference and high levels of experimental anxiety and depression may be related.

5. Possible mechanisms for neurotransmitters in shaping sexual preference

According to the classic organizational hypothesis of sexual differentiation (Cooke et al., 1998), the sex-typical programs established early in life are largely determined by circulating testosterone that, depending on the species, needs to be aromatized in specific brain areas to estrogens to exert its defeminizing (inhibiting the expression of female-related characteristics) and masculinizing (promoting the expression of male typical features) actions. In mammals, in the absence of fetal testosterone production, the brain is not defeminized and retains a cyclic gonadotropin-releasing hormone secretion required for ovulation and the expression of feminine sexual behaviors. The critical brain developmental period of sexual differentiation in rats is between prenatal day 1819 and postnatal days 1–10, which is comparable to the 23–40 week gestation period in humans (Weisz and Ward, 1980; Semple et al., 2013). Prenatal hormone exposure may influence sexual orientation in humans and also, as aforementioned, in animal models. Regarding the former, women with congenital adrenal hyperplasia (CAH), who are exposed to high levels of androgens prenatally, exhibited greater probability of being lesbian and were reported to have more non-heterosexual fantasies than the general population (Meyer--Bahlburg et al., 2008; Daae et al., 2020). Male rats, mice and ferrets castrated at birth exhibited a lower female partner preference, even if administered testosterone or estradiol when adults, as compared to those not castrated during early life. This evidence confirms the role of testosterone in organizing a male-typical partner preference (Stockman et al., 1985; Brand et al., 1991).

In addition, modifying neurotransmitters during development may also affect aspects of sexual brain differentiation. For example, injecting serotonin agonists (5-methoxytryptamine or the selective 5-$HT_{2A/2C}$ agonist, 2,5-Dimethoxy-4-iodoamphetamine hydrochloride, DOI) to male rats during the second week of postnatal life, the size of the SDN-MPOA was decreased (feminized), eliminating this typical brain sex difference (Madden et al., 2016). However, the sex difference in calbindin-SDN size was maintained regardless of serotoninergic drug treatment. This observation suggests that although gonadal hormones shape the volume of the whole SDN-MPOA, serotonin mediates only the sexual differentiation of non-calbindin cell populations within the SDN-MPOA.

Another example refers to the neuroendocrine regulation of luteinizing hormone (LH) release. The central dopaminergic system is implicated in the estrogen-induced desensitization of LH secretion to the negative estrogen feedback (Docke et al., 1987). Though still controversial, researchers also found a differential neuroendocrine responsiveness of LH secretion between homosexual and heterosexual men or women. Thus, the administration of conjugated estrogens exerted a positive feedback action on serum LH within 48 h in heterosexual women, but not in heterosexual men. Conjugated estrogens also stimulated a significant increase in serum LH in homosexual men 72 h after treatment, but this LH concentration was between that observed in heterosexual men and women (Gladue et al., 1984). After reviewing these data, the authors concluded that homosexual men showed a positive estrogen feedback on LH secretion that was never observed in heterosexual men, suggesting that the brain mechanisms controlling the pituitary secretion of LH in homosexual men is different from that of heterosexuals (Dörner et al., 1975; Dörner, 1978). However, Barbarino et al., discovered that estradiol caused a significant increase in serum LH in men (presumably heterosexuals, sexual orientation not specified) with or without gonads, suggesting that the modulation of gonadotropin secretion in men is not influenced by the perinatal exposure of the hypothalamus to androgens (Barbarino et al., 1983). In a follow up review, Baum et al., concluded that in heterosexual men (as in other male primates) the neuroendocrine mechanism mediating positive feedback effects of estrogens on LH secretion is not defeminized during the sexual differentiation process, making it a response that would not provide

evidence regarding possible neuroendocrine differences between homosexual and heterosexual men (Baum et al., 1985).

During the early postnatal period in the hypothalamus and limbic system, GABA and its rate limiting synthesis enzyme, glutamate decarboxylase (GAD), together with $GABA_A$ receptors, are more prevalent in male than in female rats, but later this sex difference disappears (Davis et al., 1999). This sex difference is estrogen-dependent, and recent evidence suggests that some of the organizational effects of estradiol action involve the GABAergic system (McCarthy et al., 2002). All these data suggest that changes in neurotransmitters during development affect sex-related anatomical and functional characteristics. Whether they are related to sexual preference or other aspects of behavior remain a matter of study.

Genetic studies point to a relationship between neurotransmitters and sexual orientation. Genome-wide association studies based on a European ancestry sample and a Chinese Han population sample revealed that *Catechol-O-methyltransferase (COMT)*, *methylenetetrahydrofolate reductase (MTHFR)* and the human *sonic hedgehog (SHH)* were related to sexual orientation (Wang et al., 2012; Yu et al., 2015; Qin et al., 2018). *COMT* is a protein of 271 amino acids (Martinez et al., 2009), regulating the catabolism of neurotransmitters such as dopamine, norepinephrine and epinephrine, as well as of catechol-estrogens (Weinshilboum et al., 1999). In addition, *MTHFR* may affect *COMT* methylation and *COMT* function (Friso et al., 2002; de Arruda et al., 2013). *SHH* is one of the key molecules that define the fate of serotonergic neurons, as well as their specification and axon pathfinding in the spinal cord and in the brain stem (Briscoe and Ericson, 2001; Cayuso et al., 2006; Xie et al., 2018). To some extent, these studies indicate that there may be a relation between sexual orientation and genes involved in the regulation of neurotransmitters.

6. Sexual fluidity

No pre- or postnatal manipulation in any male animal has resulted in subjects that, as adults, have a complete feminine sexual behavior repertoire. That is, even if treated with aromatase inhibitors or castrated and treated with hormones, some adult males display various degrees of male sexual behavior towards females (Sommer and Vasey, 2006). The same applies to masculinized females. This observation led to the idea that sexual preference in animals and sexual orientation in humans is not expressed as a binary selection, but rather as sexual fluidity. In animal models, now we know that sexual preference and behavior may vary depending upon endocrine factors during early development as well as sexually rewarding behaviors either with males or with females (Ferguson et al., 1970; Shillito, 1970; Olvera-Hernandez et al., 2019). In humans, the main mechanism responsible for gender identity and sexual orientation in males involves a direct effect of testosterone on the developing human brain, as is apparent from the psychosexual development of patients with complete androgen insensitivity syndrome (CAIS). People with this condition produce testosterone, but their bodies (including their brains) are insensitive to it as a result of mutations in the androgen receptor gene, which leads to feminization of the external sex organs and the brain (Wisniewski et al., 2000). Even if they are genetically male (with XY chromosomes), they are phenotypically women with normal feminization of secondary sexual characteristics, except for lacking female-typical amounts of axillary and pubic hair in adulthood. Regarding their sexual orientation, almost all (above 90 %) women with CAIS were heterosexual with no libido problems and with the ability to experience orgasms (this last finding illustrates that although androgens contribute to libido and orgasm in women (Sherwin, 1988), orgasms can be experienced by women with CAIS. Only 1 out of 14 (7%) women with CAIS reported gynephilic attraction i.e, attraction for women, fantasies, and experiences; however, she indicated that a lesbian orientation applied to her only in adulthood, suggesting that the development of female homosexuality was not associated with androgen exposure, but perhaps was related to having both a short vagina and a fear of vaginoplasty (Wisniewski et al., 2000).

Recently the concept of sexual fluidity in humans, which was first raised by Kinsey (Kinsey et al., 2003), got much attention. Sexual orientation is here conceptualized as a multi-dimensional construct comprising self-identified labels that could change (Mustanski et al., 2002). This goes against the classic models of sexual orientation development in which formation of sexual orientation takes place before birth (Swaab et al., 2021) and remains stable in adulthood (Money, 1976; Boucek and Kubankova, 1981). Some patients who were treated with antipsychotic drugs and developed hypersexuality were reported to change sexual orientation (Uitti et al., 1989; Klos et al., 2005). In addition, two case reports revealed a change in sexual orientation in patients suffering from Kluver-Bucy syndrome (Lilly et al., 1983). However, in both cases, such change may be related to hypersexuality rather than to sexual fluidity.

A few persons were claimed to change sexual orientation from homosexuality to heterosexuality in the framework of religiously mediated sexual orientation change (Jones and Yarhouse, 2011). On the other hand, it was shown that policies recognizing same-sex relationships may encourage women to report a sexual minority orientation (Charlton et al., 2016). Notwithstanding, the impossibility of changing sexual orientation (homosexuality to heterosexuality) in adulthood is the strongest argument against the idea that environmental influences are determinants for the establishment of sexual orientation, and against the thought that homosexuality is a life choice. Worldwide, several methods have been used to "cure" homosexuality, including hormonal treatments to adults (which involve castration and administration of testosterone or estrogens, and which affect libido but fail to change sexual orientation); psychoanalysis; apomorphine (used as an emetic) in combination with homoerotic films; psychosurgery (hypothalamic lesions); electroshocks; chemical induction of epileptic seizures; and even incarceration and torture. None of these interventions changed sexual orientation (LeVay, 2011; Balthazart, 2012).

These findings do not pretend to support the biological determinism of human behavior, particularly to the various aspects of sexuality (self-identification, attraction, fantasy and behavior). In recent studies, people were reported to change their sexual orientation to some limited degree by different interventions (Spitzer, 2003). However, reparative interventions may focus on changing the behavior rather than the innate orientation itself. Many sexual orientation reparative therapies conducted in history have indeed been reported to be based on faulty assumptions, not effective, and probably doing harm to such individuals (Haldeman, 1994; Bradshaw et al., 2015).

7. Discussion

Neuropsychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia and autism are highly prevalent (Kessler et al., 2005), contribute to 32 percent of years lived with disability and 13 percent of disability-adjusted life years (Vigo et al., 2016). As we mentioned earlier, the prevalence of these disorders is higher in sexual minorities (Yarns et al., 2016).

Neuropsychiatric disorders may be based upon altered activity in neurotransmitter systems during development or adulthood. Sexual differentiation of the brain in terms of sexual orientation is not only determined by sex hormones, but also affected by neurotransmitters. On the bases of these observations, we hypothesize that altered neurotransmitter levels during development will increase the chance for both non-heterosexual differentiation and neuropsychiatric disorders in the child's later life. This possibility may have clinical implications, because medication or other compounds that pass the placenta, when administered to pregnant women, may alter brain development and behavior of the fetus in a permanent way, leading to changes in structures involved in the control of emotionality. However, so far, no studies on the permanent effects of chemicals having long-term influences on brain development and behavior have studied the possibility of combined

non-heterosexual orientation and psychiatric problems as an outcome. A high proportion of fetuses are exposed to chemical compounds acting on neurotransmitters. According to a survey conducted in the United States, among women who had been pregnant in the past year, 25.3 % would meet criteria for a psychiatric disorder (Vesga-Lopez et al., 2008). It is estimated that approximately 10 % of those women were prescribed with a psychotropic drug during pregnancy. This average varied from 6 to 15 % between states (Hanley and Mintzes, 2014). In some rare cases, the administration of compounds during pregnancy could result in severe developmental brain disorders. For instance, studies indicate that maternal exposure to SSRIs during pregnancy increases the risk, in offspring, of autism (Andalib et al., 2017; Janecka et al., 2019) or pragmatic language disorder, and other broader behaviors that coincide with autism (Dhaliwal et al., 2020; Smearman et al., 2020; van der Veere et al., 2020), as well as anxiety and depressive behaviors in humans and in rodent models (Houwing et al., 2020; Hutchison et al., 2020). Old anti-epileptics such as diphantoin or phenobarbital, when given during pregnancy, caused a high prevalence of gender dysphoria in the children (Dessens et al., 1999). Pre-birth exposure to nicotine also increases the likelihood of lesbian daughters (Ellis and Cole-Harding, 2001). Pregnant women or laboratory animals suffering serious stress are more likely to give birth to males or females that later in life would show same-sex preference and heterotypical sexual behavior (Ward, 1972; Dörner et al., 1980; Dörner et al., 1983; Ellis and Cole-Harding, 2001; Kaiser et al., 2003; Meek et al., 2006; Hernandez et al., 2020). This effect has been explained by the raised levels of stress hormones, corticosteroids, that may affect the production of fetal sex hormones (McCormick et al., 1995; Szuran et al., 2000).

The use of oxytocin to induce and/or augment labor and delivery is on the rise. Maternal exposure to oxytocin during birth has a modest association with risk for autism in male newborns (Weisman et al., 2015). Meanwhile, babies whose mothers take drugs before their birth not only display withdrawal syndrome after birth, but also could be left with permanent brain damage. Children having intrauterine exposure to cocaine had a decreased head circumference, and exhibited more withdrawn, anxious, and depressed behaviors at 10 years of age (Richardson et al., 2013) as well as less favorable function as adolescents (Buckingham-Howes et al., 2013). These studies suggest that fetal exposure to medication that affects neurotransmitters may increase adverse neuropsychiatric outcome in newborns.

It is known now that same-sex preference does not have a single cause, but is determined by a complex interplay of different biological factors, including a genetic component (Bocklandt et al., 2006), hormonal exposure, fraternal birth order, prenatal stress and so on (Balthazart, 2020). So, the large heterogeneity in putative causal factors observed within any given sample of gay men may be underlaid by different mechanisms working to different degrees, times or combinations with each other during pre- and postnatal development (Swift--Gallant et al., 2019; Tasos, 2021). Future studies should take into account the effects that prenatally administered drugs may have on sexual orientation.

8. Conclusion

Neurotransmitters like serotonin, dopamine, oxytocin, GABA, in addition to hormonal factors, may play a part in determining sexual orientation, especially during early development. The high association between psychiatric alterations and non-heterosexual orientation suggests that neurotransmitter changes during development may have an impact on both. Medications and other chemicals given to pregnant woman may promote the development of neuropsychiatric disorders in the offspring and could lead to individuals with non-heterosexual orientation. However, there is a great need for studies on the permanent effects of chemicals affecting, in the long term, brain development and behavior, and that investigate the possibility of a combination of non-heterosexual orientation and psychiatric problems as an outcome. Since a high proportion of fetuses are exposed to chemical compounds acting on neurotransmitters, this is of great clinical importance.

Declaration of Competing Interest

The authors report no declarations of interest.

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