

Title: Is the serotonergic system altered in romantic love? A literature review and research suggestions

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Abstract

Infatuated individuals think about their beloved a lot. The notions that these frequent thoughts resemble the obsessions of obsessive-compulsive disorder (OCD) patients and that those patients benefit from serotonin reuptake inhibitors (SSRIs), have led to the hypothesis that romantic love is associated with reduced central serotonin levels. In this chapter, the literature on this topic is reviewed and suggestions for future research are made. Previous studies have shown that romantic love is associated with lower blood serotonin levels and with lower serotonin transporter densities, the latter of which has also been observed in OCD patients. Further, SSRIs have been found to decrease feelings of romantic love and the serotonin 2 receptor gene has been associated with the love trait 'mania', which is a possessive and dependent form of love. Given that serotonin 2 receptors in the prefrontal cortex have also been implicated in impulsive aggression, this suggests that stalking behavior may be associated with these receptors. In short, the serotonergic system appears to be altered in romantic love indeed. Future research is needed to identify what parts of the serotonergic system, such as which serotonergic projections, brain areas, transmission stages and receptor types, are affected in romantic love and in what way they are altered. Furthermore, challenging the serotonergic system would be useful in determining the causal relationship between central serotonin levels and feelings of romantic love. In addition, future research should specifically investigate the different aspects of romantic love, such as state, trait, requited and unrequited love and its development in time.

Introduction

Infatuated individuals and obsessive-compulsive disorder (OCD) patients resemble each other in the sense that they both have obsessions. In general, obsessions are ideas that haunt, hover and constantly invade one's consciousness (Reber & Reber, 2001). Specifically, OCD patients spend a lot of time thinking about their doubts and fears, whereas infatuated individuals spend as much as 85 percent of the day thinking about their beloved (Fisher, Aron, Mashek, Li, & Brown, 2002). This resemblance, combined with the notion that selective serotonin reuptake inhibitors (SSRIs) can relieve OCD symptoms, led Fisher et al. (2002) to hypothesize that romantic love is accompanied by reduced levels of serotonin in the brain. In this chapter, it will be discussed how this hypothesis relates to the existing literature. In addition, suggestions are made for future research that could put this hypothesis to the test and would increase our knowledge about both the serotonergic system and the neurobiology of romantic love.

Literature review

Kurup and Kurup (2003) have observed that individuals with a predisposition to fall in love had lower blood serotonin levels than did individuals without such predisposition, as evident from the fact that they had never fallen in love and had a conventional arranged Indian marriage. Thus, this study implies that lower serotonin levels are associated with increased *trait* romantic love. Furthermore, in a case study of a healthy man it was observed that *state* feelings of love were less intense and of shorter duration when taking an SSRI compared to when taking no medication (Walsh, Victor, & Bitner, 2006). Further, Marazziti, Akiskal, Rossi and Cassano (1999) have shown that infatuated compared to non-infatuated participants had a lower density of the serotonin transporter in blood platelets, a measure that is linked to the density of this transporter in the brain (Rausch et al., 2005). When the same

participants were tested again about a year later, the serotonin transporter density in the previously infatuated individual had returned to levels equivalent to the non-infatuated participants. Marazziti et al. also compared the serotonin transporter density in the infatuated participants with this density in OCD patients, and found that these were undistinguishable. Yet, because this serotonin transporter is a membrane protein that transports serotonin from the synaptic cleft back into the presynaptic neuron, a reduced transporter density implies that an increased number of serotonin molecules would be present in synapses. Still, the finding of a reduced transporter density in OCD patients is supported by positron emission tomography (PET) research in which OCD patients compared to control participants had a lower serotonin transporter density in the thalamus and midbrain (Reimold et al., 2007).

Given the resemblance between OCD patients and infatuated people, these results lead to the hypothesis that also in infatuated people the density of the serotonin transporter would be reduced in the thalamus and midbrain. In fact, it is very important to consider the locus of serotonergic changes in romantic love because the raphe nuclei in the brainstem have serotonergic projections to multiple brain structures such as the cerebellum, hippocampus, amygdala, thalamus, hypothalamus, striatum and neocortex (Kandel, Schwartz, & Jessell, 2000). Changes in the serotonergic system associated with romantic love could occur in all of these projections, only in some projections or even differently in different projections. Take schizophrenia for instance, where dopamine is too abundant in the mesolimbic dopaminergic pathway, but too scarce in the mesocortical dopaminergic pathway (Stahl, 2000).

Interestingly, the serotonergic system has also been implicated in impulsivity and aggressive behavior. The serotonergic projection to the prefrontal cortex, that would normally exert inhibitory control, appears dysfunctional in individuals who show impulsive aggression (Davidson, Putman, & Larson, 2000). Given that romantic love is usually not particularly associated with aggressive behavior or impulsivity, this suggests that the prefrontal

serotonergic projection may be unaffected by romantic love. Nevertheless, romantic love is sometimes accompanied by stalking behavior that can involve impulsivity and aggression directed towards the stalker's victim (Meloy & Fisher, 2005). So, the serotonergic projection from the raphe nuclei to the prefrontal cortex may actually play a role in stalking behavior.

Besides considering the changes in different projections or brain structures, it is also important to evaluate changes in the serotonergic system at the pharmacological level. For example, serotonergic transmission comprises different stages, such as serotonin synthesis, serotonin release from the presynaptic neuron, binding of serotonin to receptors, enzymatic degradation of serotonin in the synaptic cleft, and serotonin reuptake. Moreover, different receptor types exist, including some autoreceptors that inhibit serotonin release. The SSRIs that can alleviate OCD symptoms appear to mediate serotonergic transmission in several ways. Initially, they block the reuptake of serotonin from the synaptic cleft. The therapeutic effect, however, appears only after a few weeks and is attributed to the subsequent desensitization of the 1A and 1B autoreceptors that results in disinhibition of serotonin release from the presynaptic neuron (Stahl, 2000). Alteration or disruption of serotonergic transmission in romantic love could occur at one or more of the transmission stages and could involve one or more of the different receptor types. The above mentioned findings regarding the serotonin transporter imply changes in the reuptake stage during romantic love.

Interestingly, Emanule, Brondino, Pesenti, Re and Geroldi (2007) have not observed an association between serotonin transporter gene polymorphisms and certain love traits. This suggests that the observed differences in the serotonin transporter may occur only during state romantic love. Yet, Emanuele et al. have observed an association between the C516T polymorphism of the gene encoding the serotonin 2A receptor, which is widely distributed throughout the brain, and the love trait 'mania'. Previously, this polymorphism has been implicated in obsessive-compulsive disorder (Meira-Lima et al., 2004). Moreover, the

serotonin 2 receptors in the prefrontal cortex have been implicated in impulsive aggression (Davidson et al., 2000). Given that 'mania' is characterized as a possessive and dependent form of love (Lee, 1976), this suggests that stalking behavior may actually be associated with the serotonin 2 receptors that are located in the prefrontal cortex.

Finally, besides to obsessive-compulsive disorder and possibly romantic love, a dysfunctional serotonergic system has also been linked to depression (see e.g. D'haenen, 2001). Nevertheless, infatuated participants are rather euphoric than depressed, at least as long as the relationship is satisfactory. More research is needed to establish the differences and similarities between the serotonergic systems of depressed and infatuated individuals.

Interim summary

Above, four studies regarding the involvement of the serotonergic system in romantic love have been discussed. The results of these studies suggest that the serotonergic system is associated with romantic love although it remains unclear whether central serotonin levels are actually decreased in infatuated individuals as has been hypothesized by Fisher et al. (2002). In addition, the prefrontal serotonergic projection and the serotonin 2 receptor might be associated with the manic, stalking aspect of romantic love.

Research suggestions

The review above makes it clear that there are multiple aspects of romantic love that should be considered explicitly in future research. It is important, for example, to specify whether the topic of investigation is trait or state romantic love. Obviously, genetic studies will mostly concern trait romantic love. It is also important to distinguish between requited and unrequited love, the latter of which may be associated with depressive feelings and even stalking behavior in some individuals. Further, the time course of serotonergic changes in

romantic love has to be examined, preferably using longitudinal designs. Marazziti et al. (1999) have already shown that serotonin transporter density returns to normal values after a year, but it would be interesting to observe changes at the start of the infatuation or after rejection as well. Hereby it should be kept in mind that changes in the serotonergic system may take some time to occur, in analogy to the changes underlying the therapeutic effects of SSRIs.

So how could these issues be investigated? The functioning of the serotonergic system can be assessed by measuring levels of serotonin or its precursor or metabolites in urine, blood or cerebrospinal fluid (in order of invasiveness). Also serum prolactin elevation in response to a single dose of a serotonin agonist or precursor can be used to index central serotonin activity (e.g. Croonenberghs et al., 2007; Muldoon et al., 2007). Further, any causal relationship between serotonin and romantic love could be determined by experimentally manipulating central serotonin levels, for instance by administering a serotonin agonist or antagonist. Alternatively, central serotonin levels can be decreased by acute tryptophan depletion, which can be achieved by having participants consume a beverage containing multiple amino acids except the amino acid tryptophan (e.g. Van der Veen, Evers, Deutz, & Schmitt, 2007), which is the precursor of serotonin. Likewise, central serotonin levels can be increased by using a beverage containing high levels of tryptophan compared to other amino acids (e.g. Bjork, Dougherty, Moeller, Cherek, & Swann, 1999).

Finally, the neuroimaging technique PET would be especially suitable for comparing the serotonergic system of infatuated individuals with that of non-infatuated individuals or patients with OCD or depression. In PET studies, a radioactive substance that has a high affinity for a certain binding site is injected, and detectors then measure where in the brain that radioactive substance accumulates. In research concerning the serotonergic system and romantic love, the radioactive substance would be selected for its binding to a certain

serotonin receptor or transporter, thereby making it possible to investigate the locus of changes in the different aspects of the serotonergic system.

Conclusion

The few studies that have examined the relation between serotonin and romantic love have shown that the serotonergic system is probably dysfunctional in infatuated individuals.

However, more research is needed to identify the exact locus of these changes, that is to determine which serotonergic projections, brain areas, transmission stages and receptor types are altered in romantic love. To this end, crosstalk between the different disciplines such as neuroimaging, genetics and pharmacology is needed. Finally, future research will have to specifically investigate the different aspects of love, such as state or trait love, requited and unrequited love and its development in time.

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