Archives Italiennes de Biologie, 149: 265-268, 2011.

NGF and romantic love

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ABSTRACT

Romantic love is the catalyst behind the spread of the human life. The neurobiology of love embraces the hypothesis that what we call "romantic attachment" or "romantic love" may be at least in part the expression of biological factors. A corollary of this hypothesis states that it is possible to learn much about the nature of human love by studying the molecules involved in the expression of social and affiliative behaviours. Under this theoretical framework, we have investigated the changes in plasma neurotrophin levels in subjects with early-stage romantic love. A positive association between the intensity of early romantic feelings and serum levels of nerve growth factor (NGF) has been identified. These findings link love with biologically relevant pathways for neuron survival and illuminate the biochemical correlates of such a complex feeling that so deeply affects our own lives. The progresses in the neurobiology of love suggest that this kind of research may open a new window onto our understanding of the very nature of human romantic bonding.

Key words

Romantic love • Neurotrophins • Nerve growth factor • Social bonds

1. Introduction

"Love is a mistery". This old adage has been challenged by modern science once that neurobiology has developed to the point at which progress could be made on the very nature of human romantic bonding. The hope for the future is that a synergy between psychology, sociology, comparative biology, neuroimaging, biochemistry, and genetics would lead to an improved understanding of how humans mate (Fisher et al., 2006; Stárka, 2007; Zeki, 2007; Debiec, 2007; Stein and Vythilingum, 2009). A better comprehension of the biological basis of romantic relationships should not be regarded merely as a scholar question. Romantic love is the catalyst behind the spread of the human life, and romantic involvement affects many – if not all – aspects of our personal and public lives (Esch and Stefano, 2005). Hence, research on the biological facets of love has important implications for sociology, psychology, and philosophy. From the point of view of medicine, and of psychiatry in particular, a better comprehension of human love might hold promise to reduce a terrible burden taken by unrequited love on our society, i.e. suicides due to disturbed love affairs in young people (Emanuele, 2009). Psychological autopsy studies and analysis of suicide notes have clearly demonstrated that unrequited love does actually represent a common trigger for suicide (Lester et al., 2004; Bhatia et al., 2006). Suicidal ideation after a disappointed romantic love has been also reported, and much of the impetus for discerning the biological basis of human love in our research group has been prompted by a friend's suicide after a disturbed love affair (Emanuele and Politi, 2006). From these observations it clearly emerges that romantic relationships could be somewhat a double-edged sword in a person's life. When reciprocated, intense romantic love is accompanied by feelings of overwhelming joy and has been compared to a hypomanic state (Marazziti and Cassano, 2003). In contrast, unreciprocated love can result in a host of

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negative emotions and destructive behaviours including anger, desire for revenge, low self-esteem, obsessionality, hopelessness, feelings of social isolations, loneliness, anguish, depression, stalking, violence, and even suicides or homicides (Fisher et al., 2010). Under these circumstances, the understanding of the normal "physiology" of human mating behaviour represents the necessary premise to the study of "pathological" love from its mild-to-moderate expressions (obsessionality, ruminations, jealousy) to the most severe forms (depression, stalking, violence, and suicide).

Although there is a voluminous literature discussing the cultural and psychological aspects of human love, its neurochemical facets have hitherto been left relatively unexplored. Is there any biological correlate of the overwhelming feelings typically elicited by early stage intense romantic engagement? Even though studies assessing the role of biology in love have been sparse (Marazziti and Canale, 2004), romantic bonding in humans has a deep biological root that plays a pivotal role in the perpetuation of human life. We thus argue that any attempt to explain human mating behaviour that ignores the biological factors behind love (genes, hormones, brain circuitries) should be actually regarded as incomplete.

2. Nerve growth factor increases in early-stage intense romantic love

In an effort to shed more light on the biochemical changes associated with early-stage intense romantic love, we have measured serum levels of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophins 3 (NT-3) and 4 (NT-4) in a total of 58 subjects who had recently fallen in love (Emanuele et al., 2006). Levels of neurotrophins observed in subjects in love were compared with those of two comparison groups, consisting of subjects who were either single or were already engaged in a long-lasting relationship. The background hypothesis of the study was that neurotrophins, originally described as key regulators of synaptic plasticity and neural survival during development and at adulthood, could also play an important role in anxiety, emotions and behavioural modifications. Only subjects whose relationships have begun within the previous 6 months were considered eligible for inclusion in the "early-stage romantic love group". In addition, all subjects were required to spend at least 4 h per day in thinking about the romantic partner. Axis-I and axis-II disorders, axis-I diagnosis of first degree relatives and psychotropic medication intake led to immediate exclusion from the study. All eligible subjects were required to fill the short hand version of the passionate love scale (PLS) (Hatfield and Sprecher, 1986), a reliable psychometric tool capable of quantifying the intensity of romantic love. The first control group consisted of 58 age- and sex-matched subjects who were already engaged in a long-lasting (mean duration: 49 ± 19 months) relationship. The second control group comprised a total of 58 singles with no romantic relationship. Serum levels of NGF, BDNF, NT-3 and NT-4 were determined using enzyme-linked immunosorbent assays.

Results showed that NGF levels were significantly increased in subjects in love [mean (SEM): 227 (14) pg/ml] than in either those with a long-lasting relationship [123 (10) pg/ml, $p < 0.001$] or singles [149 (12) pg/ml, $p < 0.001$] (Emanuele et al., 2006). On the other hand, the concentrations of BDNF, NT-3 and NT-4 did not differ among the study groups. Notably, in the "early-stage intense romantic love" group, a significant positive correlation was found between plasma NGF levels and the intensity of the romantic relationship as assessed by the PLS ($p = 0.007$). However, no such correlation was found between PLS and other NTs. In subjects in love who – after 12-24 months – maintained the same relationship but were no longer in the same mental state to which they had referred during the first evaluation, plasma NTs levels were retested. The results of this analysis showed that, albeit maintaining their relationship, PLS scores in these subjects significantly declined. Similarly, NGF concentrations demonstrated a significant decrease of 45.1% (from 227 (14) pg/ml to 125 (9) pg/ml, $p < 0.001$). Neither the levels of NGF nor the intensity of romantic love at the first assessment were predictive in terms of romantic attachment during this second evaluation.

3. Potential links between nerve growth factor and early intense love

Taken together, the results of our study clearly showed that levels of NGF, but not of other neurotrophins, were significantly increased in the early phase of

a romantic love. In addition, at the beginning of a romance, we found a significant positive correlation between levels of NGF and the intensity of romantic feelings at the beginning of a romance. Although the mechanisms behind this selective increase of NGF remain unclear, these findings indicate that raised NGF levels when falling in love could be related to specific emotions typically associated with intense early-stage romantic love, such as emotional dependency and/or euphoria. NGF is a neurotrophic peptide that has been originally described as a key regulator in the survival and maturation of neurons in the peripheral and central nervous system (Levi-Montalcini et al., 1996). In addition to its neurotrophic activity, *in vivo* experiments have shown that NGF may increase circulating levels of adrenocorticotropin and corticosterone, thus inducing activation of the HPA axis (Otten et al., 1979; Angelucci, 1994). Evidence derived from *in vitro* experiments suggested that NGF may induce an increase of both release and content of hypothalamic vasopressin (Scaccianoce et al., 1993), a neuropeptide which plays a pivotal role in the formation of social bonding (Winslow et al., 1993; Kendrik, 2004). We therefore speculated that NGF can play a role in the molecular mechanisms of early human romantic love by acting as a fine modulator of distinct endocrine functions.

An alternative possibility is that NGF plasma concentrations in subjects in love can be increased secondarily in a stress-dependent manner. In this regard, previous studies have demonstrated that circulating NGF levels increase following stressful events and anxiety-associated behaviour (Aloe et al., 1994; Hadjiconstantinou et al., 2001; Branchi et al., 2004). Therefore, the typical NGF elevation occurring in early-stage intense romantic love can reflect the stressful conditions and/or arousal associated with the beginning of a social bond, which may in turn be useful to overcome neophobia. Of note, when we assessed NGF levels for a second time (12-24 months later) in the subjects who maintained the same relationship but were no longer in the same altered mental state, we found no significant difference in the circulating concentrations of this neurotrophin as compared with those measured in the two comparison groups. These results clearly suggest that the neurochemical bases of early-stage romantic love may be substantially different from those of longer-term romantic relationships.

4. NGF, love, and analgesia

A very recent study (Younger et al., 2010) has shown that the early-stage intense phase of human romantic love is associated with a reduced perception of experimental painful stimuli, a finding that disappeared in subjects who maintained the same relationship but were no longer in the same altered mental state. The authors concluded that a better understanding of the analgesic pathways involved in this phenomenon may allow us to identify new targets and methods for producing effective pain relief. These experimental findings have striking parallels with our biochemical findings concerning the link between NGF and human romantic love (Emanuele et al., 2006). Intriguingly, NGF has been show to be an essential peptide for sensory neurons (Watson et al., 2008). In addition, peripheral administration of NGF was found beneficial in clinical trials of sensory neuropathy (McArthur et al., 2000). Finally, NGF regulates the number and efficacy of sensory neurons, resulting in enhanced opioid susceptibility towards better pain control. So far, we have a link between NGF and love, and a link between NGF and pain. The study by Younger et al. (2010) closes the loop by providing the link between pain and love. NGF, love, and pain form a sympathetic triad, mirroring one another's complexity.

5. Concluding remarks

Despite considerable progress in recent years, love is an enduring scientific taboo and continues to appear an atypical topic for empirical studies (Emanuele and Politi, 2006). Romantic feelings are often seen as to be too evanescent for evidence-based researchers, especially in the biomedical field. This is nonetheless unfortunate, given the pivotal role played by love in our lives and the potential links between unrequited love, depression, obsessionality, and even suicide (Emanuele, 2009; Fisher et al., 2010).

Our data have clearly demonstrated that circulating levels of NGF, but not of other neurotrophins, are increased among subjects in love, suggesting an important role for this molecule in the 'social chemistry' of human beings (Emanuele et al., 2006). The specificity of NGF increase during early-stage love clearly indicates that this neurokine can play a pivotal role in the formation of novel bonds, whereas it does not appear to play a major role in their main-

tenance. Although no psychophysiological explanation can be directly inferred from our observational study, we speculate that NGF could exert this effect by acting as a modulator of diverse endocrine functions, including HPA axis activation and secretion of the prosocial hormone vasopressin.

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