Psychosocial factors in the aetiology of unipolar depression

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Abstract

Psychosocial factors are an important contributor to the aetiology of unipolar depression. This paper reviews the evidence for the contribution of different psychosocial factors and provides an overview of the proposed neurobiological mechanisms underlying the link between psychosocial factors and depression. Implicated psychosocial factors fall into three interrelated groups: life events, socioeconomic status and social support. The life events most strongly linked with depression are bereavement, childhood maltreatment and disability or medical illness. Others include refugee status, workplace stressors and obesity. Studies linking low socioeconomic status with depression are conflicting. There is strong evidence for an association between lack of social support and depression. Multiple neurobiological mechanisms linking psychosocial factors to depression have been suggested but evidence remains limited. The current evidence points to increased activity in the hypothalamic-pituitary axis, epigenetic modifications of key genes and inflammatory processes, but other mechanisms being explored include reduced monoamine concentration, and structural changes to the limbic system, prefrontal cortex, cingulate cortex and hippocampus. There is overlap between these mechanisms.

Introduction

Psychosocial factors contribute significantly to the aetiology of unipolar depression, with the estimated heritability accounting for only 37% of disease occurrence (1). The psychosocial factors which have been implicated in the aetiology of unipolar depression fall into three interrelated groups: life events, socioeconomic status and social support. The neurobiological mechanism by which these factors lead to depression is poorly understood but is the subject of ongoing research.

Life events

Negative life events, or life stressors, are among the most studied risk factors for unipolar depression. The relevance of a life event to the risk of depression may depend on a number of characteristics, including its perceived undesirability, the extent to which the individual has control over it, its magnitude, the degree to which it is life threatening and its duration (2). The strength of association of many life events or stressors with depression varies according to age, with stronger associations found in the age groups in which the usual occurrence of a given stressor is lowest and therefore least expected (3).

Strong evidence exists for the role of bereavement (4, 5), disability or medical illness (6), and childhood maltreatment (7) in the aetiology of depression. A meta-analysis of 20 prospective cohort studies on risk factors for depression in the elderly found an odds ratio of 3.3 for bereavement, 2.5 for disability, and 1.8 - 2.1 for medical illness (8). A meta-analysis of eight cohort studies investigating the relationship between maltreatment in childhood and depression reported an odds ratio of 2.03 (7).

The relationship between bereavement and depression appears to be one of the most significant. In part, this may be attributable to the overlapping presentations of normal grief and depression. Factors associated with depression, rather than normal grief, include the individual's coping mechanisms, a traumatic or unexpected death, and the extent to which the bereavement results in social isolation (9).

Another implicated life stressor is refugee status. A meta-analysis of 35 population-based cross-sectional studies found a depression prevalence of 44% among refugees (10). A more recent cross-sectional study

of depression among Syrian refugees in a Turkish refugee camp reported a prevalence of 37% (11). Workplace stressors may also play a role in the aetiology of depression. A systematic review of 16 prospective cohort studies investigating the relationship between job-related psychosocial factors and depression indicated that exposure to perceived psychosocial stressors at work is related to an increased risk of depression (12). The factor for which the relationship was strongest was job strain, which was defined as a combination of high work demands and low level of control. A cross-sectional study of 1169 people in three European countries suggested that an effort-reward imbalance at work is associated with depression (13).

Obesity is another proposed factor in the aetiology of depression, particularly among adolescents and also persons up to 50 years of age (3). A meta-analysis of 15 longitudinal cohort studies found an association between obesity and depression; obesity increased the risk of depression with an odds ratio of 1.55 and depression was predictive of the development of obesity (14).

Socioeconomic status

Low socioeconomic status has been associated with depression, and it may also be related to poorer access to health and mental health services, increased exposure to negative life events, and fewer social support factors (15). A prospective cohort study of 9193 individuals indicated that low socioeconomic status was associated with increased rates of depressive symptoms in all age groups. Indicators of low standards of living showed the strongest associations, with odds ratios reported for depression at age 18 ranging from 1.20 for manual social class to 1.74 for material hardship (16). In another prospective cohort study investigating the risk factors for first-onset unipolar depression in 3170 individuals, the effects of poverty were reduced when controlling for the degree of social isolation, suggesting that the effect of socioeconomic status on depression may be mediated through social support factors (17). However, a systematic review of 25 primarily cross-sectional studies investigating the risk factors for chronic depression concluded that the influence of socioeconomic status was inconsistent (18). Another systematic review of 71 cross-sectional and longitudinal studies on risk factors for depression in the elderly similarly found that the relationship between low education level or low income and depression was inconsistent (19). In short, the evidence for the role of socioeconomic status remains inconclusive.

Social support

A lack of social support and, in particular, a lack of relationships that provide emotional support, have been implicated in the aetiology of depression. This may be because social support both directly enhances psychological well-being and reduces or buffers the negative impact of the life stressors described above (2). A systematic review of 25 primarily cross-sectional studies investigating risk factors for chronic depression found that low social support, negative social interaction and low social integration were all linked to chronic depression (18). A systematic review of 71 cross-sectional and longitudinal studies on risk factors for depression in the elderly found associations with both quantitative and qualitative aspects of social networks, including low contact frequency, smaller network size, being unmarried and having a lack of social support (19).

Mechanisms

Identifying the neurobiological processes that underlie the association between psychosocial factors and depression may reveal pathways through which the risk for depression can be mitigated. Proposed mechanisms are summarised below.

Increased hypothalamic-pituitary-adrenal (HPA) axis activity

Increased HPA axis activity has been implicated as a link between psychosocial factors and depression. Early life stress, such as prolonged maternal separation, has been shown to be associated with an increased risk of depression in mice (20). Mice exposed to maternal deprivation had marked increases in stress-induced corticosteroid secretion with increased depressive symptoms and memory deficits (21).

It is hypothesised that early stress causes hypersensitivity to glucocorticosteroids, an effect that per-

sists into adulthood (22). A sensitisation effect has been described in the literature, whereby individuals require less stress to set off certain behaviours with time, making them more prone to depressive symptoms. This effect was observed in a study (female twin pairs n = 292, non-twin sisters n = 46) which found that childhood adversity and negative life events in adulthood increased negative affect to daily stressors (23).

Epigenetic modification of key genes

Recent studies have proposed a role for the epigenetic modification of certain gene regulatory regions in the neurobiology of depression. One review of 25 papers (6 animal studies, 19 human studies) examined the relationship between DNA methylation and stress in the context of depression. The effect of chronic stress was predominantly investigated through animal studies focusing on genes related to the HPA axis. Many of these studies drew the conclusion that stress-related DNA methylation resulted in increased production of corticotrophin-releasing factor (CRF), adrenocorticotrophic hormone and glucocorticoids. Thus, epigenetic changes could help to explain the link between increased HPA activity and depression described in the previous section. Potential epigenetic targets included the CRF gene and the glucocorticoid receptor NR3C1. Those studies focusing on the association between depression and DNA methylation were mainly human studies concentrating on neurotransmission. Important genes included those involved in serotonergic transmission (SLC6A4) and brain-derived neurotrophic factor (BDNF) (24). The role of decreased serotonergic neurotransmission in the aetiology of depression is well recognised. A systematic review of 19 studies found an association between SLC6A4 methylation and exposure to various negative life events in children aged under 18 years (25). A prospective cohort study of 132 adolescents (26) demonstrated that adolescents with a lower socioeconomic status displayed increased methylation of the SLC6A4 promoter gene ($p=0.02$). This methylation was able to predict increased threat-related amygdala activity in all groups and, in those with a positive family history of depression, predicted the manifestation of depression in later life ($p=0.02$). It may be that a positive family history exposes adolescents to a higher degree of life adversity, accounting for the significance in this subset. A second prospective cohort study of 338 African American adolescents had similar findings, showing that poorer socioeconomic status was significantly correlated with increased methylation of the SLC6A4 promoter. The strength of the correlation varied between sexes, between multiple CpG methylation sites, and between short and long serotonin transporter gene alleles (27). This may suggest that the association is complex and affected by gene-environment interactions.

Animal studies have shown increased methylation of the promoter of the nuclear receptor NR3C1 in the adrenal and pituitary glands (29), and demethylation of the CRF promoter in the paraventricular nucleus in rats exposed to stress (30). Resultant decreased expression of glucocorticoid receptors in the hypothalamus causes reduced negative feedback along the HPA axis and hence increased activity. This may explain the reported hypercortisolaemia in severe depression (31).

BDNF is a neurotrophin involved in neuronal growth and plasticity. Stress has been shown to cause histone methylation of promoters of the BDNF gene, reducing BDNF protein expression, which has been associated with depression.

Inflammatory processes

There is a body of evidence supporting the role of inflammatory mechanisms in the aetiology of depression (32). Furthermore, the role of inflammation has been implicated as a mediator between psychosocial factors and depression (33).

A prospective cohort study of 1000 patients demonstrated co-occurrence of depression and elevated levels of C-reactive protein (CRP) in those with a history of childhood maltreatment (34). In another prospective cohort study of 147 adolescent females, in those subjects exposed to childhood adversity the development of depression was accompanied by increases in CRP and interleukin-6 (35).

Other mechanisms

Structural changes have been described in studies of chronic stress (36) and childhood maltreatment (37),

with induction of degeneration of hippocampal neurons.

Roles for cholecystokinin (38), tachykinins (39), and spinophilin, synaptophysin and myelin basic protein (40) have been proposed in the neurobiology of depression, but only in single studies. Further studies are needed before any strong conclusions can be drawn.

Psychosocial factors have been proposed to impact gene expression through miRNA regulation (41, 42); however, further studies are also necessary to characterise this association.

Conclusion

Numerous psychosocial factors are implicated in the aetiology of depression. The mechanisms by which these contribute to the disease process, whilst still not elucidated fully, overlap, so that more than one mechanism may be involved in the action of each of the factors. This suggests that the manipulation of each of these factors could be of benefit in the overall treatment of depression.

References

1. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. American Journal of Psychiatry. 2000 Oct 1;157(10):1552-62.

2. Bruce ML. Psychosocial risk factors for depressive disorders in late life. Biological Psychiatry. 2002 Aug 1;52(3):175-84.

3. Schaakxs R, Comijs HC, van der Mast RC, Schoevers RA, Beekman AT, Penninx BW. Risk factors for depression: differential across age? The American Journal of Geriatric Psychiatry. 2017 Sep 1;25(9):966-77.

4. Florence C, Emmanuelle L, Florence BL, Mathilde H, Viviane KM. Bereavement-related depression: Did the changes induced by DSM-V make a difference? Results from a large population-based survey of French residents. Journal of Affective Disorders. 2015 Aug 15;182:82-90.

5. Bruce ML, Kim K, Leaf PJ, Jacobs S. Depressive episodes and dysphoria resulting from conjugal bereavement in a prospective community sample. The American Journal of Psychiatry. 1990 May 1;147(5):608.

6. Geerlings SW, Beekman AT, Deeg DJ, Van Tilburg W. Physical health and the onset and persistence of depression in older adults: an eight-wave prospective community-based study. Psychological Medicine. 2000 Mar;30(2):369-80.

7. Li M, D'arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychological Medicine. 2016 Mar;46(4):717-30.

8. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. American Journal of Psychiatry. 2003 Jun 1;160(6):1147-56.

9. Aziz R, Steffens DC. What are the causes of late-life depression? Psychiatric Clinics. 2013 Dec 1;36(4):497-516.

10. Lindert J, von Ehrenstein OS, Priebe S, Mielck A, Brähler E. Depression and anxiety in labor migrants and refugees–a systematic review and meta-analysis. Social Science & Medicine. 2009 Jul 1;69(2):246-57.

11. Acarturk C, Cetinkaya M, Senay I, Gulen B, Aker T, Hinton D. Prevalence and predictors of posttraumatic stress and depression symptoms among Syrian refugees in a refugee camp. The Journal of Nervous and Mental Disease. 2018 Jan 1;206(1):40-5.

12. Bonde JP. Psychosocial factors at work and risk of depression: a systematic review of the epidemiological evidence. Occupational and Environmental Medicine. 2008 Apr 16.

13. Pikhart H, Bobak M, Pajak A, Malyutina S, Kubinova R, Topor R, Sebakova H, Nikitin Y, Marmot M. Psychosocial factors at work and depression in three countries of Central and Eastern Europe. Social Science & Medicine. 2004 Apr 1;58(8):1475-82.

14. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Archives of General Psychiatry. 2010 Mar 1;67(3):220-9.

15. Areán PA, Reynolds III CF. The impact of psychosocial factors on late-life depression. Biological Psychiatry. 2005 Aug 15;58(4):277-82.

16. Joinson C, Kounali D, Lewis G. Family socioeconomic position in early life and onset of depressive symptoms and depression: a prospective cohort study. Social Psychiatry and Psychiatric Epidemiology. 2017 Jan 1;52(1):95-103.

17. Bruce ML, Hoff RA. Social and physical health risk factors for first-onset major depressive disorder in a community sample. Social Psychiatry and Psychiatric Epidemiology. 1994 Jul 1;29(4):165-71.

18. Hölzel L, Härter M, Reese C, Kriston L. Risk factors for chronic depression - a systematic review. Journal of Affective Disorders. 2011 Mar 1;129(1-3):1-3.

19. Vink D, Aartsen MJ, Schoevers RA. Risk factors for anxiety and depression in the elderly: a review. Journal of Affective Disorders. 2008 Feb 1;106(1-2):29-44.

20. Anisman H, Zaharia MD, Meaney MJ, Merali Z. Do early-life events permanently alter behavioral and hormonal responses to stressors? International Journal of Developmental Neuroscience. 1998 Jun 1;16(3-4):149-64.

21. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmühl Y, Fischer D, Holsboer F, Wotjak CT, Almeida OF, Spengler D. Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nature Neuroscience. 2009 Dec;12(12):1559.

22. Mirescu C, Peters JD, Gould E. Early life experience alters response of adult neurogenesis to stress. Nature Neuroscience. 2004 Aug;7(8):841.

23. Wichers M, Schrijvers D, Geschwind N, Jacobs N, Myin-Germeys I, Thiery E, Derom C, Sabbe B, Peeters F, Delespaul P, Van Os J. Mechanisms of gene-environment interactions in depression: evidence that genes potentiate multiple sources of adversity. Psychological Medicine. 2009 Jul;39(7):1077-86.

24. Bakusic J, Schaufeli W, Claes S, Godderis L. Stress, burnout and depression: A systematic review on DNA methylation mechanisms. Journal of Psychosomatic Research. 2017 Jan 1;92:34-44.

25. Provenzi L, Giorda R, Beri S, Montirosso R. SLC6A4 methylation as an epigenetic marker of life adversity exposures in humans: a systematic review of literature. Neuroscience & Biobehavioral Reviews. 2016 Dec 1;71:7-20.

26. Swartz JR, Hariri AR, Williamson DE. An epigenetic mechanism links socioeconomic status to changes in depression-related brain function in high-risk adolescents. Molecular Psychiatry. 2017 Feb;22(2):209.

27. Beach SR, Dogan MV, Brody GH, Philibert RA. Differential impact of cumulative SES risk on methylation of protein–protein interaction pathways as a function of SLC6A4 genetic variation in African American young adults. Biological Psychology. 2014 Feb 1;96:28-34.

28. Fuchikami M, Morinobu S, Segawa M, Okamoto Y, Yamawaki S, Ozaki N, Inoue T, Kusumi I, Koyama T, Tsuchiyama K, Terao T. DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression. PLOS One. 2011 Aug 30;6(8):e23881.

29. Witzmann SR, Turner JD, Mériaux SB, Meijer OC, Muller CP. Epigenetic regulation of the glucocorticoid receptor promoter 17 in adult rats. Epigenetics. 2012 Nov 13;7(11):1290-301.

30. Elliott E, Ezra-Nevo G, Regev L, Neufeld-Cohen A, Chen A. Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. Nature Neuroscience. 2010 Nov;13(11):1351.

31. MacKenzie EM, Odontiadis J, Le Mellédo JM, Prior TI, Baker GB. The relevance of neuroactive steroids in schizophrenia, depression, and anxiety disorders. Cellular and Molecular Neurobiology. 2007 Jul 1;27(5):541-74.

32. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature Reviews Immunology. 2016 Jan;16(1):22.

33. Cattaneo A, Macchi F, Plazzotta G, Veronica B, Bocchio-Chiavetto L, Riva MA, Pariante CM. Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. Frontiers in Cellular Neuroscience. 2015 Mar 31;9:40.

34. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Archives of General Psychiatry. 2008 Apr 1;65(4):409-15.

35. Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biological Psychiatry. 2012 Jul 1;72(1):34-40.

36. Magariños AM, Li CJ, Toth JG, Bath KG, Jing D, Lee FS, McEwen BS. Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons. Hippocampus. 2011 Mar 1;21(3):253-64.

37. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. American Journal of Psychiatry. 2013 Oct;170(10):1114-33.

38. Becker C, Zeau B, Rivat C, Blugeot A, Hamon M, Benoliel JJ. Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystokinin. Molecular Psychiatry. 2008 Dec;13(12):1079.

39. Husum H, Wörtwein G, Andersson W, Bolwig TG, Mathé AA. Gene–environment interaction affects substance P and neurokinin A in the entorhinal cortex and periaqueductal grey in a genetic animal model of depression: implications for the pathophysiology of depression. International Journal of Neuropsychopharmacology. 2008 Feb 1;11(1):93-101.

40. Leussis MP, Andersen SL. Is adolescence a sensitive period for depression? Behavioral and neuroanatomical findings from a social stress model. Synapse. 2008 Jan;62(1):22-30.

41. Babenko O, Golubov A, Ilnytskyy Y, Kovalchuk I, Metz GA. Genomic and epigenomic responses to chronic stress involve miRNA-mediated programming. PLOS One. 2012 Jan 24;7(1):e29441.

42. Suderman M, Borghol N, Pappas JJ, Pereira SM, Pembrey M, Hertzman C, Power C, Szyf M. Childhood abuse is associated with methylation of multiple loci in adult DNA. BMC Medical Genomics. 2014 Dec;7(1):13.