There is a new form of antidepressants – triphasic antidepressants

Dopamine (specifically the mesocortical pathway) has some evidence of dysfunction in depression. Bupropion and atypical antipsychotics act on this pathway.

A second NT that has received interest with regards to depression is glutamate. In the 1990’s it was found that NMDA-R antagonists produce antidepressant-like action (Trullas and Skolnick, 1990). Therefore, it is postulated that depression is the result of elevated glutamate content.

Mitani et al. (2006) supported this by finding increased glutamate in the cerebrospinal fluid as well as a correlation between HAM-D scores and glutamate concentration.

Further to this, Maes et al. (1998) found that antidepressants decreased plasma glutamate levels.

Glutamate is responsible for ionotropic communication and is the major excitatory neuron of the brain. It is a difficult NT to modulate.

Ketamine is a drug with glutamatergic properties and has been found to produce rapid symptom relief although not long-lasting in treatment-refractory depression (Zarate et al., 2010)

Endocrine abnormalities:

- It has also been suggested that the cause of depression comes from endocrine abnormalities
- This hypothesis came about from the observation that approximately half of the individuals with Cushing’s syndrome suffer from major depression and this depression remits when cortical hypersecretion is corrected.
- From this, research has looked further into the cortisol-depression association.
- Cortisol liberates glucose. It interacts with neurons - there are lots of cortisol receptors that are usually unoccupied, they fill when you are stressed making the neurons work very efficiently. You have them in the frontal lobes (thinking) and hippocampus (remembering).
- Primary roles are in mobilising physiological resources:
  - Increasing heart rate and blood pressure
  - Activating hepatic energy stores
  - Diverting resources away from inflammatory responses and to more immediate needs
  - Primes the brain to be alert, remember and learn
- HPA inputs from the limbic system, PFC, SHT, NA can all modulate
- Stress increases cortisol release
- Roughly 50% of depressed patients have increased plasma cortisol secretion in the 24-hour cycle
- The dexamethasone suppression test looks at suppressing cortisol through inhibiting ACTH release at pituitary level. This test found that about 50% of inpatients with depression do not show normal cortisol suppression.
- In addition, it has been found that some classes of antidepressants increase expression of glucocorticoid receptors. Glucocorticoid receptors regulate the amount of cortisol.
- Corticotrophin-releasing hormone has a role in cortisol secretion and acts as a neurotransmitter in limbic regions of the brain where it regulates responses to stress
- In animals CRH induces changes in sleep and appetite – paralleling depression

The depressions