Karolinska Institutet

Institutionen för klinisk neurovetenskap

Sex Steroids and Gene Variants in Bipolar Disorder

AKADEMISK AVHANDLING
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Abstract

Bipolar disorder is a chronic, cycling disorder affecting circa 2% of the population and whose pathophysiology is still largely unknown. It has been suggested that common treatments used for bipolar disorder have effects on the sex steroids yet sex steroids have also been shown to have widespread effects in the brain in systems of relevance to bipolar disorder. For example, DHEAS and progesterone have opposing effects on the glutamatergic and GABAergic systems essential for the regulation of other brain processes. The enzymes which are involved in the interconversions between these compounds are affected by a number of factors including polymorphisms in the genes coding for these enzymes. Papers 1-3 examine common polymorphisms in *AKR1C4*, *HSD3B2* and *SRD5A1,* their relationships with 8-9 am serum hormone concentrations as well as to retrospectively but systematically collected data on symptoms which in animal and human studies have shown a possibility of connection to neurosteroid abnormalities. All investigations including history taking was done in euthymic phase of bipolar 1 or 2 disorders and included all available sources of information such as chart review and third party information. In paper 1, men but not women had lower serum progesterone concentrations during euthymic phase of bipolar disorder if they had exhibited manic irritability as opposed to euphoric mania. A gene variant of *AKR1C4* was associated with lower progesterone concentrations and polymorphisms of this gene were also more frequent in the males with prior irritability during mood elevation. Paper 2 showed that these same polymorphisms that increased risk in men *reduced* the risk for paranoid ideation during mania in women. However in men, DHEAS and progesterone were both lower and this coupled at a trend level to a polymorphism in the *HSD3B2* gene. In paper 3, depressive psychomotor agitation was coupled in both men and women to polymorphisms in *SRD5A1*. Yet only in men did one of the polymorphisms correspond to increased progesterone, a finding which was in line with the finding of higher progesterone if men had showed depressive psychomotor agitation.

Testosterone has different effects to progesterone and DHEAS in the brain and has been implicated in psychosis, having effects on the dopamine system. In paper 4, parameters measuring testosterone effects at different points in development were investigated in women with bipolar disorder who had exhibited psychotic features and compared with those in women with bipolar disorder without such features as well as healthy control women. The A allele at rs6152 of the Androgen Receptor gene was associated with a greater risk of having had psychotic symptoms and was at a trend level associated with an earlier debut of psychotic symptoms. The D2:D4 finger ratio which is believed to be a measure of prenatal testosterone milieu correlated with age of onset of psychosis indicating that high testosterone in the foetus predisposed the individual to an earlier psychosis onset but not to getting psychotic per se. A possible gene by drug interaction was found whereby the G allele rs6152 was associated with much higher bioavailable testosterone in the presence of neuroleptics. Upon further investigation this was explained by lower SHBG (sex hormone binding globulin) even in the presence of low doses of atypical neuroleptics.

Taken together these studies suggest the involvement of sex steroids in mediating risk to particular phenotypes of presentation of bipolar disorder, rather than bipolar disorder itself. The symptoms correspond to those regarded to be of the so called mixed states. Whilst the studies are of reasonable size in ascertaining hormonal differences the studies are small with respect to the genetic data and need to be replicated in larger samples.

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