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Genetics of Bipolar Disorder

PL ACADEMIC RESEARCH

1. Introduction

Many psychiatric diseases run within families and kinship. A high hereditary factor of mental disease was proven early through numerous family, twin and adoption studies. Important mental diseases such as Schizophrenia, Depression, Addiction, Autism, and Chorea Huntington have a strong genetic predisposition. With the exception of Chorea Huntington, those mental diseases do not show monogenetic pathogenesis, but a polygenetic inheritance. An orchestra of multiple, potentially interacting genes with small effects and incomplete penetrance lead to predisposition. Numerous possible susceptibility genes for psychiatric diseases are still unidentified and it is not exactly known how they interact to lead to illness.

Although molecular psychiatry is still in its infancy it is possible that in the future psychiatric genetics might help to draw exact lines between psychiatric diagnoses, which may lead to restructuring of nosology [Burmeister et al. 2008]. Furthermore, molecular genetics give insight in pathogenetic mechanisms, which will help to find targets for development of new medication and laboratory markers. Additionally, the knowledge of inheritance could lead to potent prevention strategies. However, one has to illuminate the gene-environment-interactions to detect plans against disease onset. Though molecular psychiatry still has to overcome initial difficulties, it is an attempt to review the genetics of bipolar affective disorder [Craddock et al. 2005].

1.1 Bipolar Affective Disorder

1.1.1 History and Symptomatology of Bipolar Disorder

Over centuries psychiatric terminology was confusing. Among the first to provide potential concepts were Araeteus from Cappadocia (50-130 A.D.), Jean Pierre Falret (1794-1870) and Jules Baillarges (1809 –1890). Over a century the essence of manic-depressive insanity was typically explained in Falret's term "folie circulaire" and Bailarger's "folie a double forme" [Benazzi et al. 2006; Haustgen et al. 2006]. However, their concepts were not sufficiently defined and

not discerned enough [Alexander and Selesnick 1969; Angst et al. 2001]. Emil Kraepelin was the first to successfully coin the terms. He introduced the dualism of schizophrenia ("dementia praecox") and bipolar disorder ("manic depressive insanity") in a clear way. He described bipolar disorder as "manic depressive insanity" [Jablensky et al. 1999; Hippius et al. 2008]. Bipolar disorder is a mood disorder which includes depressive and manic episodes. Manic episodes are characterized by either elevated or dysphoric mood or a raised energy level. Other typical symptoms of mania are delusion of grandeur, logorrhea, racing thoughts, loss of social inhibitions, reduced requirement of sleep, hypersexuality, increased goal-directed activity or agitation, impulsive or high-risk behaviors for instance reckless spending of money. Manic episodes lead to marked impairment of social or occupational functioning. In contrast to manic episodes are depressive episodes, which are characterized by vital sadness, anhedonia, low self-esteem, reduced activity, loss of energy, listlessness, as well as reduced concentration. Yet elevated activity in line with agitated depression is possible. Another feature of depression is disturbance of sleep, especially insomnia, early awaking and disruption of sleep. Usually appetite is reduced, whereas also hyperphagia can occur in atypical depression or seasonal affective disorder. Further devastating symptoms are the inability of making decisions, loss of interests and social retraction, even social isolation might occur. Suicide ideation may arise in major depression, as well as suicide attempts and suicide in the last resort [Nabuco de Abreu et al. 2009; Hyong et al. 2008; Kapfhammer et al. 2008]. The change of depressive episodes with marked manic episodes is diagnosed as bipolar I disorder while a change of hypomania and depression is classified as bipolar II disorder in DSM-IV. Hypomanic states are milder and do not cause impairment. Courses of manic disease without depressive episodes are rare [Schulte-Körne 2008; Barnett 2009]. A special subtype of bipolar disorder is called rapid cycling and is defined by switching of mood episodes (depression, mania and hypomania), to remission or to the opposite pole within short time periods. Rapid cycling is characterized by at least 4 episodes within 12 months by DSM-IV. Patients with ultra rapid cycling might even switch within days and ultra ultradian rapid cycler within hours [Bauer et al. 2008; Barnett et al. 2009].

1.1.2 Pharmacotherapy

Psychopharmacological therapy of bipolar disorder is primarily based on mood stabilization with either Lithium or antiepileptics or antipsychotics. Severe acute mania might also need additional sedating benzodiazepines (e.g. Lorazepam, up to 15mg per day necessary in acute mania; usual daily dose 1-10mg per day)

temporary. But supplementary use of benzodiazepines should be considered cautiously, because they bear the risk of addiction. In severe depressed states additional antidepressant therapy might be unavoidable. Nevertheless, mild episodes of depression should be treated only by mood stabilizers and non-pharmacological therapy (e.g. behavior therapy, sports and ergotherapy), because antidepressants bear the risk of switching from depressed to manic states and should be considered carefully. Since guidelines change with the current scientific knowledge we want to refer to the following other sources [Benkert and Hippius 2011]:

1. A very detailed version of the treatment guidelines for bipolar disorder by the DGBS („Deutsche Gesellschaft für Bipolare Störungen“) and DGPPN („Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde“) of May 2012:
   http://www.leitlinie-bipolar.de/wp-content/uploads/2012/10/S3_Leitlinie-Bipolar_V1_5.pdf
2. Download of the current “ÖGBP Konsensus Statements” by the ÖGBP („Österreichische Gesellschaft für Neuropsychopharmakologie und Biologische Psychiatrie”):
   http://www.medizin-medien.at/dynasite.cfm?dsmid=58914
3. CANMAT (“Canadian Network for Mood and Anxiety Treatments”) guidelines:
   http://www.canmat.org/guides.php
4. Guidelines of the APA (“American Psychiatric Association”):
   http://psychiatryonline.org/guidelines.aspx
5. Last but not least we recommend current editions of psychopharmacological books (e.g. Benkert, Hippius; “Kompendium der Psychiatrischen Pharmakotherapie, 8.Auflage, Springer Verlag”) for further detailed information, since we give only a short summary here.

Mood Stabilization

Lithium

Lithium has been the gold standard of mood stabilization since 1949 and is efficient for acute and prophylactic treatment in bipolar disorder, beside it has suicide prophylactic effects [López-Muñoz et al. 2007; Fountoulakis et al. 2010]. One mechanism of action is the influence towards signal transduction systems. One target is the inositolphosphatepathway. Phosholipase C catalyzes the building of inositoltriphosphate and diacylglycerol. Those second messengers lead to activation of proteinkinase C (PKC), as well as intracellular calcium release from the

endoplasmatic reticulum. Finally calcium mediates several effects like synthesis and release of monoaminergic neurotransmitters. Lithium inhibits proteinkinase C and influences adenylylcyclase and G-proteins. Furthermore Lithium and antiepileptics inhibit the inositolmonophosphatase, which consequently leads to depletion of inositol. Lithium also shows neuroprotective effects and seems to induce neurogenesis. Beside Lithium inhibits voltage-gated sodium-channels like many antiepileptics (Valproinacid, Carbamazepine and Lamotrigine). Lithium, as well as antiepileptics, enhance the GABAergic neurotransmission and strengthen the serotonergic neurotransmission [Benkert and Hippius 2011]. Lithium is also a potent inhibitor of glycogen-synthase-kinase-3 (GSK3), which is a serine–threonine kinase that intermediates various intracellular signaling pathways [Bhat et al. 2004]. GSK3b phosphorylates and stabilizes the orphan nuclear receptor Rev-erba, a negative component of the circadian clock. Lithium treatment of cells leads to rapid proteasomal degradation of Rev-erba and activation of the clock gene ARNTL. Interestingly Arntl heterodimers with the clock protein Npas2 and the dimer binds to promoter e-boxes of MAOA, which leads to transcription of MAOA. Finally the expressed enzyme mono-amine-oxidase-A inactivates dopamine [Yin et al. 2006]. Since mechanisms of Lithium's antimanic effects are not totally clear, a genome wide association study tried to discover genes involved in Lithium response. They found an involvement of GRIA2, a glutamate/alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionate (AMPA) receptor gene. Nevertheless, further investigation is necessary [Perlis et al. 2009].

In acute mania the Konsensus Statement of the ÖGPB has recommended a "loading dose" of 900mg Lithium per day. Lithium-concentrations from 1,0 till 1,2mmol/L should be reached in acute mania. The recommended daily dose of Lithium lies between 600 and 1200mg in acute states of mania. Severe acute mania might need addition of antipsychotics or transiently benzodiazepines, because Lithium shows initially given a latency of some weeks. Mild or moderate acute states of mania can be treated with Lithium monotherapy [Benkert and Hippius 2011]. Side effects of Lithium are nausea, tremor, tiredness, polyuria, vertigo, obstipation or diarrhea, weight gain, edema, alopezia, sexual dysfunction, acne, cognitive deficits, arrhythmia or ECG changes in general, hypothyroidism or nephrotoxicity, which can range from mild reduced kidney function till diabetes insipidus, nephrotic syndrome or renal failure [Anditsch et al. 2009; Benkert et al.2011; DGPPN guidelines 2012]. Because of the small therapeutic index, symptoms of beginning intoxication like tremor, vertigo, diarrhea, enhanced reflexes and disorientation over 1,6mmol/L can be expected. Typical symptoms of Lithium intoxication (over 2,5mmol/L) are neurological symptoms, epileptic seizure and dysrhythmia [Konsensus Statement ÖGPB 2008]. Mild Lithium intoxication (1,5-2,0 mmol/L) can be treated by intravenous application

of physiologic salt solution and Sodium substitution for increasing the renal Lithium clearance. Severe intoxications (over 2,0 mmol/L) need hemodialysis. Increased effect of Lithium may be due to reduced Lithium clearance and reduced renal perfusion via reduced sodium intake, non-steroidal antiphlogistics (e.g. Diclofenac), Metronidazol, ACE-inhibitors, tetracyclics or diuretics [Rothenhäusler et al. 2004]. Before beginning a Lithium therapy the following analyses are necessary: complete blood count, renal function parameters, thyroid values, blood pressure, ECG, thyroidal investigation, pregnancy test and measuring of weight [Rothenhäusler et al. 2004]. Since patients with bipolar disorder response differently to Lithium treatment, the "ConLiGen-Consortium" was formed to investigate the relationship between SNPs of susceptibility genes and treatment outcome, in a large GWAS with 1200 bipolar patients [Schulze et al. 2010].

Antiepileptics

Antiepileptics (Valproinacid, Carbamazepine and Lamotrigine) inactivate voltage-gated sodium-channels. Beside they influence many signaltransduction pathways similar to Lithium e.g. they inhibit proteinkinase C. Depletion of inositol seems to be a shared effect as well [Benkert and Hippius 2011]. The ÖGPB Konsensus Paper states, that Carbamazepine (e.g. Neurotop®, Tegretol®) and Valproinacid (e.g. Convulex® and Depakine®) are good alternatives for the gold standard Lithium. Both are approved for treatment of acute mania, as well as prophylaxis. If monotherapy is not potent enough the combination Lithium and Valproinacid is recommended. Severe acute mania might need early addition of antipsychotics to antiepileptics. Lamotrigine and Carbamazepine are not admitted for treatment of acute mania, but for prevention of affective episodes. Lamotrigine prevents depressed episodes in bipolar disorder. Interestingly Lamotrigine is supposed to mediate its antidepressant effects among other things via BDNF [Benkert and Hippius 2011; Li et al. 2011]. Side effects of Valproinacid are nausea and vomiting, vertigo, tremor, elevated liver parameter, weight gain, pancreatitis, hair loss, thrombocytopenia, polycystic ovary syndrome and SLE. Valproinacid shows superior onset of action than Lithium and better tolerability with the same efficacy. Therapy with Valproinacid should begin with a loading dose of typically 1000mg per day (exactly 20-30mg/kg body weight). Then the recommended daily dose of Valproinacid for treatment of acute mania lies between 1200 and 3000mg. The maximum daily dose is 3000mg. Therapeutic serum levels of Valproinacid should be between 75 and 120 µg/ml. Side effects of Carbamazepine are sedation, vertigo, ataxia, nausea, tremor, hyponatraemia, allergic reactions, leucopenia, thrombopenia, aplastic anaemia and elevation of liver enzymes, as well as hepatitis. Carbamazepine should be dosed between 600

and 1200mg per day in acute mania. Plasma levels of Carbamazepine from 6 to 12ng/ml should be reached. The maximum daily dose of Carbamazepine is 3000mg. Furthermore Carbamazepine shows interactions with Phenobarbital, Primidone, Zidovudine, Carbamazepine, Lamotrigine, anticoagulans, which increase the plasma levels. The suggested daily dose of Lamotrigine lies between 12,5 and 500mg. The maximum daily dose is 700mg. A slow increase of Lamotrigine is necessary to prevent severe skin reactions (week 1 and 2: 25mg per day, week 3 and 4: 50mg per day, then increase of 50-100mg per 2 weeks). Side effects of Lamotrigine (e.g. Lamictal®) are severe skin reactions (e.g. Stevens-Johnsons-Syndrom), blood count changes, diplopia, tiredness, nausea and vertigo. Furthermore Lamotrigine shows interaction with CYP3A4 inductors (decrease of plasma level), as well as Valproinacid (increase of plasma level, cave: skin reaction) [Anditsch et al. 2009; Konsensus Statement ÖGPB 2008; Fountoulakis et al. 2010; Benkert and Hippius 2011]. Other anticonvulsants (like Gabapentin, Levetiracetam, Oxcarbazepine, Tiagabine, Topiramate and Zonisamide) show more or less positive results in case reports and small studies, but do not have the admission for treatment of mania [Anditsch et al. 2009; Benkert and Hippius 2011].

Atypical Antipsychotics

Atypicical antipsychotics are dopamine receptor inhibitors and have been widely used in therapy of schizophrenia. However, nowadays they are also established in mood stabilization in bipolar disorder. Antimanic effects of Aripiprazole (e.g. Abilify®), Olanzapine (e.g. Zyprexa®), Quetiapine (e.g. Seroquel®), Risperidone (e.g. Risperdal®), Ziprasidone (e.g. Zeldox®) have been shown in several studies against placebo. All atypical antipsychotics are admitted in treatment of acute mania, while Aripiprazole, Olanzapine and Quetiapine are admitted for prevention of manic states too. While only Quetiapine is admitted in prophylaxis of manic, as well as depressed states. In contrast Ziprasidone is the only approved antipsychotic drug for mixed states. Antipsychotics are also especially recommended in dysphoric mania, as well as severe mania with psychotic symptoms. Combination therapies with atypical antipsychotics and Lithium or atypical antipsychotics and Valproinacid are more potent than Lithium- or Valproinacid-monotherapy in severe mania [Benkert and Hippius 2011]. Furthermore the side effects are responsible for choosing the right antipsychotic agent. Side effects of antipsychotics are generally spoken anticholinergic effects (e.g. obstipation or urinary retention), hyperprolactinemia, weight gain, metabolic syndrome, extrapyramidal side effects and very seldom malignant neuroleptic syndrome (the latter shows extrapyramidal effects e.g. akinesia, rigor; hyperthermia; tachycardia; mutism; catatonia; disturbance of consciousness; rhabdomyolysis). Extrapyramid-

al side effects like akinesia (inability to initiate movement), akathisia (feeling of motor restlessness), acute dystonic reactions (e.g. muscular spasms of tongue; torticollis; oculogyric crisis), pseudoparkinsonism and tardive dyskinesia (involuntary asymmetrical movements of the muscles) have been common in patients treated with first generation antipsychotics (e.g. Haloperidole). But second generation antipsychotics lead rarely to these severe side effects. Nevertheless there are ways to resolve or milden extrapyramidal side effects (e.g. according to the symptom anticholinergic agents like Biperiden/Akineton® or dose reduction or benzodiazepines). Quetiapine shows virtually zero risk of extrapyramidal signs, but similar to Olanzapine, high risk of gaining weight via increase of appetite. Beside Quetiapine and Olanzapine show the highest degree of sedation, while in contrast Aripiprazole or Ziprasidone do not lead to tiredness. In contrast Aripiprazole shows more often of nervousness, agitation and akathisia [Konsensus Statement ÖGPB 2008; Fountoulakis et al. 2010]. The following daily doses are recommended in acute mania: 15-30 mg Aripiprazole, 10-20mg Olanzapine, 400-800mg Quetiapine, 2-6mg Risperidone, 80-160mg Ziprasidone. Interactions: Olanzapine shows interactions with CYP1A2-inhibitors and anticholinergic agents (plasma level increase), as well as CYP1A2-inductors (reduced plasma level). Quetiapine shows interactions with CYP3A4-inductors (decrease of plasma level) and CYP3A4-inhibitors like HIV-protease-inhibitors, antifungal agents, Erythromycin, Clarithromycin and Nefazodone (increase of plasma levels). Aripiprazole shows enhanced plasma levels if given with CYP2D6-inhibitors or CYP3A4-inhibitors, as well as reduced plasma levels if combined with CYP3A4-inductors. Risperidone shows the risk of serotonin-syndrom if given with serotonergic agents. Beside Risperidone shows enhanced risk of akathisia in combination with Fluoxetine, Fluvoxamine and Paroxetine. Like other antipsychotics it shows the risk of hypotonia together with antihypertensives. Antipsychotics also enhance the risk of arrhythmias if given with QTc-time-increasing agents like Amiodarone, Sotalol, Erythromycin, Clarithromycin, antimycotics, Methadone, triptans, 5-HT3-antagonists and others [Anditsch et al. 2009; Benkert and Hippius 2011].

Antidepressant Therapy

Antidepressants helped to release numerous suffering people from the burden of depression. Although antidepressants lead to recoverment for the bigger part of patients, around 30-40% of the individuals do not show full response. It is also difficult to dose antidepressants ideally, because patients with bipolar disorder are at risk to switch from depressive to manic states. Especially potent dual acting antidepressants like NASSA and NARI, as well as older tricyclic or tetracyclic

antidepressants show high risk for switching. Instead SSRI and NDRI should be favored. If possible, mild depressive episodes should only be treated by mood stabilizers and psychotherapy. Since patients show various responses to psychopharmacological treatment, genetic profiles might help to create optimal individual treatment plans in future directions [Benkert and Hippius 2011; Konsensus Statement ÖGPB 2008; Kato et al. 2009].

Selective Serotonin Reuptake Inhibitors (SSRI)

SSRI inhibit the serotonin transporter (encoded by the gene SERT on 17q11.1-q12), which mediates the active transport of serotonin into neurons, enterochromaffin cells, platelets and other cells. In the central nerve system the transporters are located in perisynaptic membranes of nerve terminals and dendritic arbors in close proximity to serotonin-containing cell bodies in the midbrain and brain stem raphe nuclei [Murphy et al. 2004]. The serotonin transporter mediates the quick removal of serotonin in the synaptic gap after neuronal stimulation. Blockage of the transporter by SSRI leads to longer maintenance of serotonin in the synaptic gap, because reuptake into presynaptic vesicles is not possible. Potent serotonin reuptake inhibitors (SSRIs) include Fluoxetine (e.g. Fluctine®, Mutan®; daily dose: 20-60mg), Fluvoxamine (e.g. Floxyfral®; daily dose 100-300mg), Paroxetine (e.g. Seroxat®; daily dose: 20-50mg), Sertraline (e.g. Tresleen®, Gladem®; daily dose: 50-200), Citalopram (e.g. Seropram®; daily dose: 20-60mg) and Escitalopram (e.g. Cipralex®; daily dose: 10-20mg). Side effects of SSRI are nervousness, sleeping disorder (especially in the first two weeks), platelet aggregation inhibition, nausea, headaches, loss of appetite, sexual dysfunction, hyponatraemia and QT-prolongation [Rothenhäusler et al. 2004; Anditsch et al. 2009; Kapfhammer et al. 2008; Konsensus Statement ÖGPB 2008; Benkert and Hippius 2011].

NASSA (Noradrenaline and Serotonin Specific Antidepressant)

Mirtazapine (e.g. Remeron® and Mirtabene®; daily dose: 30-45mg), a sedative antidepressant, leads via inhibition of central α_2-receptors and inhibition of negative feedback loops, which usually inhibit the release of the neurotransmitters, to better availability of noradrenaline and serotonine in the synaptic gap. Furthermore it inhibits 5-HT_2 and 5-HT_3 receptors, as well as the H_1 receptor. The latter is responsible for the sedating effect. Common side effects are increased appetite, weight gain, tiredness and headaches. Rare side effects are hypotension, vertigo, nausea, tremor, dry mouth, edema and nightmares. Beside Mirtazapine can lead to increase of liver enzymes, blood count changes and exanthema seldom