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mediated by an activation of dopamine D1 and D2 receptors. Financial support: CAPES, CNPq, IBN-Net (Brazil).

References

P2.d.022 Gene by drug interactions in genome-wide pharmacogenetic data: a NEWMEDS study
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Purpose of study: Antidepressant treatment for major depressive disorder has uncertain outcome with currently unpredictable individual variation in therapeutic response. Previous pharmacogenetic studies have reported genetic variants that are associated with response to antidepressants overall. However, differential predictors of better response to one drug than another drug are needed to inform the selection of treatment in individual cases. The current study is the largest comparative antidepressant pharmacogenetic study to date investigating genetic determinants of differential response to antidepressants with differing mechanisms of action (serotonergic versus noradrenergic). We undertook a traditional gene-by-drug interaction test; however unequal distribution of drug type (serotonergic versus noradrenergic) and an association of the drug variable to underlying population structure resulted in reduced statistical power in the interaction test. Thus a novel method was tested to remove the effect of these two issues on statistical power of the test. This work is being undertaken as part of the Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) project, a large multicentre European Union funded collaboration between academia and industry.

Method: 1893 unrelated individuals of white European ancestry were administered either a serotonergic antidepressant (n=1271) or a noradrenergic antidepressant (n=622) as part of previous pharmacogenetic studies. GeneChip n=820; GenoPac n=512; Pfizer=345; Glaxo-Smith Kline=134; GODS=82. Individuals were genotyped using Illumina Human 610-quad chip or 660W-quad chip and underwent routine quality control. Quality-controlled genome-wide data were available for 1790 individuals. Outcome was measured as a censored continuous variable (percentage improvement). Drug (a binary variable) was unequally distributed (2:1) and linked to population structure in the combined sample. A subset of the sample randomly allocated to one of the two drugs whose distribution of the drug variable was equal and independent of population structure was used as a standard. Multiple statistical strategies were undertaken to investigate their effects on gene-by-drug interactions, including traditional interaction analyses, and linear regression with flipped outcome (i.e. a zero-centred outcome variable reversed in one drug group).

Result: Routine test of gene-by-drug interaction through multiple regression with partialled product terms produced a distribution of test statistic that was significantly below the expected uniform distribution (lambdamedian=0.9077) in the entire sample but performed well in the randomly allocated sub-sample (lambdamedian=1.0015). Analysis with flipped outcome showed a uniform distribution of p-values in both the entire sample (lambdamedian=0.9991) and randomly allocated sample (lambdamedian=1.0001). There was good agreement between the two analyses, with high correlations of –log10 p-values in both samples (0.9512 and 0.7950 [Pearson’s]). The SNP with the lowest p-value in the flipped outcome analysis, rs280060 (p=7.08∗10−6), was located on chromosome 4, 170kb upstream of the nearest gene SMARCAD1.

Conclusion: Traditional gene-by-drug interaction analyses are over-conservative. A simple approach is offered that tests interaction with reasonable assumptions and produces a uniformly distributed unbiased statistic. The proposed novel approach will be useful to detect differential predictors of response to different drugs, which is the most useful information for personalizing treatment. The results are preliminary and further validation is needed before method is adopted.

Disclosure statement: Tansey, Guipponi, CM. Lewis and Uher declare that they have no financial or other relevant conflicts of interest. G Lewis has received occasional fees for speaking from the pharmaceutical industry. Wendland is a full time employees of Roche. McGuffin has previously received consultancy fees and honoraria for participating in expert panels from pharmaceutical companies including Lundbeck and GlaxoSmithKline, but has not had such income in the last 3 years.

P2.d.023 Agomelatine reverses the decrease in hippocampal cell survival induced by chronic mild stress
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Depression is thought to be associated with impairment in hippocampal neurogenesis. Agomelatine is a melatonergic (MT1/MT2) receptor agonist and 5-HT2C receptor antagonist with demonstrated antidepressant properties in animal models and in clinical studies. Further, agomelatine was shown to enhance adult hippocampal neurogenesis in animals under basal conditions (1). Yet, little is known about effects of agomelatine in the brain exposed to chronic stress as a risk factor for major depressive disorder. Recently, we described agomelatine-induced changes on neuronal activity and adult neurogenesis in the hippocampus of rats subjected to chronic footshock stress (2).

In order to better characterize the actions of agomelatine in the stress-compromised brain, here we investigated its effects on hippocampal neurogenesis in the chronic mild stress (CMS) paradigm proposed as an animal model of depression.
Adult male rats were subjected to various mild stressors for 5 weeks, and treated intraperitoneally (i.p.) with amphetamine (40 mg/kg) daily 2 hours prior to the dark phase during the last 3 weeks of the stress period. Control rats were either untreated or treated with vehicle (1% hydroxyethylcellulose). The sucrose preference test was performed weekly to measure anhedonia, and the marble burying test was carried out at the end of the experiment to measure an anxiety-induced behavioral response to environmental challenge. In order to determine effects on different stages of the neurogenesis process, i.e. cell proliferation, newly-born neuron maturation and cell survival, immunohistochemistry for nuclear protein Ki-67, doublecortin (DCX) and bromodeoxyuridine (BrdU, 300 mg/kg i.p. single injection 4 days before the start of experimental stress) was respectively performed. All measurements were done in the dentate gyrus of the hippocampus.

In our model, the CMS paradigm did not change sucrose preference among the groups; however, it increased marble burying behavior, indicating enhanced anxiety. Agomelatine treatment reduced burying behavior, but this effect did not reach statistical significance. Interestingly, this stress model differentially affected distinct stages of the neurogenesis process. Whereas CMS did not influence the rate of cell proliferation among the groups, it significantly decreased the newborn cell survival (p < 0.05) in the hippocampal dentate gyrus in both untreated and vehicle-treated animals. Also, CMS significantly decreased hippocampal DCX expression (p < 0.05) in both groups of control rats. Importantly, chronic treatment with agomelatine completely normalized stress-affected cell survival (p < 0.05) whereas it did not influence the rate of cell survival in vehicle-treated animals. Finally, in stressed animals, chronic agomelatine partly reversed reduced DCX expression as compared to vehicle (p < 0.05).

Taken together, these data show that the CMS paradigm differentially affects distinct stages of the adult hippocampal neurogenesis process, and that agomelatine has beneficial effects on the stress-affected cell survival and newly-born neuron maturation in the dentate gyrus. Thus, agomelatine at antidepressant dose counteracts the deleterious effects of chronic stress on hippocampal neurogenesis in an animal model of depression, which is in line with our previous findings.

References

Effect of antidepressants on depression, anxiety and cognition in relation with pain models

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Monoamine reuptake inhibitors are mainly used for the treatment of depression. Moreover, substantial evidence supports that the monoamine-enhancing agents have also a genuine anxiolytic and analgesic effect. However, it is not well establish the relationships of the serotonergic and/or noradrenergic system in all these effects. Here, we explore the effect of the different classes of antidepressants in models of depression, anxiety, cognition and pain in relation with the mechanism of action these compounds. [1]

The antidepressants studied were reboxetine (RBX, 4–64 mg/kg, i.p.) (selective NA reuptake inhibitor, SNRI), fluoxetine (FLX, 4–64 mg/kg, i.p.) (selective 5-HT reuptake inhibitor, SSRRI) and the dual SHT/NA reuptake inhibitor antidepressants duloxetine (DLX, 4–64 mg/kg, i.p.), milnacipran (MLN, 4–64 mg/kg, i.p.) and venlafaxine (VLX, 4–64, 80, 96 mg/kg, i.p.). They were investigated in CD-1 mice by means of the forced swimming test (FST) and tail suspension test (TST) as paradigms aimed at screening antidepressants; the dark-light and marble burying test as models of anxiety; the Morris water maze test was and 8-arm radial maze as cognition models and the hot-plate test and acetic acid test (AA) as phasic and tonic nociceptive models respectively. The results showed: Depression models: (i) FST: RBX 4–64 mg/kg, FLX 32, 64 mg/kg, DLX 4–64 mg/kg, MLN 32, 64 mg/kg and VLX 16–64, 80, 96 mg/kg significantly decreased the immobility time versus saline, as expected. (ii) TST: RBX 4–64 mg/kg, FLX 32, 64 mg/kg, DLX 4–64 mg/kg, MLN 32, 64 mg/kg and VLX 16–64, 80, 96 mg/kg significantly decreased the immobility time respect to saline. Anxiety models: (i) Dark–light test: DLX 4–64 mg/kg, and VLX 64, 80, 96 mg/kg significantly increased the light time versus saline. (ii) Marble burying test: RBX 64 mg/kg, FLX 16–64 mg/kg, DLX 8–64 mg/kg, MLN 32, 64 mg/kg and VLX 32, 64, 80, 96 mg/kg significantly decreased the number of marbles buried versus saline. Cognition models: Memory was not impaired by antidepressant drugs, except at high doses in (i) Morris test: VLX 80 mg/kg and (ii) 8-arm radial maze: RBX 64 mg/kg. Pain models: (i) Hot plate test: RBX 16–64 mg/kg, FLX 32, 64 mg/kg, MLN 64 mg/kg and VLX 80, 96 mg/kg significantly increased the latency time versus saline. (ii) AA test: RBX 4, 16–64 mg/kg, FLX 16–64 mg/kg, DLX 8–32 mg/kg, MLN 32, 64 mg/kg and VLX 64, 80, 96 mg/kg significantly reduced the number of writhing. Therefore, the results showed that the SNRI, reboxetine and the SSRRI, fluoxetine, exerted their antidepressant and analgesic effect in a similar range of doses. Reboxetine and venlafaxine at high doses have a cognitive impairment and this may due to sedative effect of both antidepressants. However, the antidepressant effect of dual antidepressants started at lower doses compared to the anxiolytic and analgesic effect. These data suggest that noradrenergic and/or serotonergic neurotransmission have different influence on the antidepressant, anxiolytic and analgesic profile of antidepressants.

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