Vetenskapsrådet

Ansökan

2015-03-26

2015-02515_1 **Eriksson, Elias**

Information om sökande

Namn: Elias Eriksson

Dr-examen: 1985-05-17

Födelsedatum: 19560807

Akademisk titel: Professor

Kön: Man

Arbetsgivare: Göteborgs universitet

Medelsförvaltare: Göteborgs universitet

Hemvist: Neurovetenskap och fysiologi, inst för

Information om ansökan

Utlysningsnamn: Forskningsbidrag Stora utlysningen 2015 (Medicin och hälsa)

Bidragsform: Projektbidrag

Sökt inriktning: Fri

Ämnesområde:

Projekttitel (svenska): Selektiva serotoninåterupptagshämmare: gåtor och kontroverser

Projektstart: 2016-01-01

Projektslut: 2020-12-31

Sökt beredningsgrupp: MH-D2

Klassificeringskod: 30215. Psykiatri

Nyckelord: Depression, Anxiety, Premenstrual dysphoric disorder, Serotonin, Antidepressants

Sökta medel

År:	2016	2017	2018	2019	2020
Belopp:	2 310 000	2 310 000	2 310 000	2 310 000	2 310 000

Beskrivande information

Projektinformation

Projekttitel (svenska)*

Selektiva serotoninåterupptagshämmare: gåtor och kontroverser

Projekttitel (engelska)*

Selective serotonin reuptake inhibitors: enigmas and controversies

Abstract (Engelska)*

Used by approximately 7% of the population for the treatment of depression and a variety of other psychiatric conditions, the selective serotonin reuptake inhibitors (SSRIs) remain highly controversial – 25 years after they were introduced there is hence still no consensus regarding the pivotal question if they actually exert any specific antidepressant effect. After having conducted meta-analyses on all placebo-controlled trials once conducted by the drug companies to establish the antidepressant effect of the SSRIs, influential debaters have thus came to the conclusion that these drugs are at best marginally superior to placebo, and that this superiority is probably not due to a specific pharmacological action, but the result of an enhanced psychological placebo effect elicited by side effects making the patient realize that he/she has not been allotted placebo.

Given the gravity of the disorders for which they are used, most of which are associated with enhanced mortality and markedly reduced life quality, and since there are no reasons to assume that any novel treatment will emerge in a foreseeable future that will render the SSRIs redundant, it must be considered a task of the utmost importance to settle the current controversy regarding the efficacy, or lack of efficacy, of these medications.

Even among researchers believing the SSRIs to be effective, most would probably agree that our knowledge on their mechanism of action remains disturbingly poor. Thus, while there is little doubt that the serotonin transporter indeed is their primary molecular target, it remains (for example) unclear i) why they display a sluggish onset of action when used for some conditions (such as depression and anxiety disorders) but not for others (such as premenstrual dysphoria), ii) if their net influence on serotonin output (at acute and continuous administration, respectively) is best described as facilitating or dampening, iii) how their various therapeutic effects of these drugs seen in patients relate to the physiological influence of brain serotonergic transmission on behaviour, and iv) which of the many different serotonin receptor subtypes that mediate the wanted and unwanted effects of these drugs.

The aims of this project hence are twofold:

Project A) By conducting post hoc analyses on a unique data bank comprising patient level-data from most drug company-sponsored placebo-controlled SSRI trials ever conducted we hope to resolve the issue of their alleged ineffectiveness as well as a number of other related questions. The first results from these analyses suggest that the antidepressant effect of the SSRIs has until now been grossly underestimated.

Project B) By means of a combination of animal and clinical experiments we also hope to shed further light on a number of issues of fundamental importance for the understanding of the mechanism of action of the SSRIs in different indications, and of how the clinical effects of these substances may relate to the physiological role of brain serotonin.

Populärvetenskaplig beskrivning (svenska)*

Antidepressiva farmaka av kategorin selektiva serotoninåterupptagshämmare (SSRI) används av ca 7% av befolkningen och det är långt fler som någon gång har medicinerat med dem. För sjukdomarna depression, tvångssyndrom, paniksyndrom, social fobi, generaliserat ångestsyndrom och premenstruell dysfori ses de som farmakologisk förstahandsbehandling.

Trots att dessa medel, av vilka det första utvecklades i Sverige, har varit i bruk i 25 år, råder det dock fortfarande oenighet om huruvida de alls utöver någon specifik farmakologisk effekt. Många menar således att den mest korrekta tolkningen av de kontrollerade studier som utförts avseende effekterna av SSRI-preparaten är att dessa medel endast är obetydligt mer effektiva än placebo (om ens det). Detta ifrågasättande har även påverkat de myndigheter som utfärdar behandlingsrekommendationer, vilka numera således uppvisar en långt mer skeptisk syn på SSRI-medlen än tidigare.

Också bland dem som är övertygade om att dessa farmaka faktiskt fungerar skulle de flesta medge att vår kunskap om varför de utövar effekt fortfarande är starkt begränsad. Det är t ex inte känt varför en och samma läkemedelsgrupp kan användas vid ett så pass stort antal disparata tillstånd, eller varför den gynnsamma effekten vid vissa sjukdomar, t ex paniksyndrom, inte inträder förrän efter veckor av behandling, och ibland föregås av förvärrade symptom, men vid andra indikationer, t ex premenstruell dysfori, inträder omedelbart.

Ej heller är det klarlagt om effekten av SSRI-medlen på den serotonerga transmissionen vid akut respektive kontinuerlig tillförsel kan bäst beskrivas som en facilitering eller dämpning av den serotonerga aktiviteten. Vilka subtyper av serotonerga receptorer som är involverade i de olika effekterna av SSRI är likaså okänt, och ej heller har vi klart fört oss vilket samband som föreligger mellan det fysiologiska inflytandet av serotonin å ena sidan och den kliniska effekten av SSRI-preparaten å den andra. Att det föreligger nära interaktioner mellan könshormoner och den serotonerga transmissionen är tydligt, men hur detta samspel är organiserat, och vilka som är dess konsekvenser, är också otillräckligt klarlagt.

Vi har länge intresserat oss för SSRI-medlens effekter. Första gången en stark hämmare av återupptaget av serotonin (klomipramin) introducerades för behandling av den vanligt förekommande ångestsjukdomen paniksyndrom skedde detta t ex på initiativ från vår forskargrupp. Och det var också vi som först visade att serotoninåterupptagshämning är en effektiv metod för behandling av premenstruell dysfori, och att den gynnsamma effekten vid detta tillstånd uppträder mycket snabbare än den gynnsamma effekten vid depression och ångestsjukdom. Vi har också bedrivit en omfattande djurexperimentell forskning med syfte att belysa underliggande mekanismer för SSRI-medlens olika effekter, som t ex deras hämmande effekt på sexuell funktion, deras ångest-provocerande effekt (vid akut tillförsel) och deras gynnsamma effekt vid premenstruell dysfori och andra tillstånd präglade av ilska och irritabilitet.

Det nu aktuella projektet har två syften. För det första hoppas vi, genom att efteranalysera data från ett stort antal placebo-kontrollerade studier, kunna slutligt avgöra den segdragna kontroversen kring huruvida SSRI-medlen faktiskt fungerar. Preliminära resultat från dessa analyser indikerar att SSRI-medlen i själva verket utövar en mycket robust antidepressiv effekt, vars styrka fram till nu har underskattats till följd av att studierna varit olycklig designade.

För det andra är det vår ambition att i kombinerade kliniska och djurexperimentella studier öka kunskapen om varför SSRI-medlen fungerar. Denna del av projektet utgår från en av oss formulerad hypotes enligt vilken en viktig fysiologisk uppgift för signalämnet serotonin under evolutionen har varit att påverka benägenheten att, i händelse av fara, skifta känsloläge, från sådana emotioner som leder till aggression, sexuell aktivitet och födointag till sådana emotioner, ffa rädsla, som leder till flykt. Enligt denna teori kan de effekter som ibland ses vid akut SSRI-tillförsel, t ex minskad irritabilitet, minskat sexuellt intresse, minskat födointag och ökad ångest, ses som uttryck för en förstärkt serotonerg aktivitet, medan de som är fullt uttalade först efter lång tids behandling, som den antidepressiva och ångestdämpande effekten, snarare är resultatet av en adaptiv nedreglering av ett anxiogent inflytande

Projekttid

Antal år för projektet*

5

Beräknad projekttid*

2016-01-01 - 2020-12-31

Klassificeringar

Välj minst en och upp till tre SCB-koder som motsvarar inriktningen för ditt projekt, i prioritetsordning.

Välj SCB-kod i de tre nivåerna och klicka sedan på det nedre plustecknet för att spara ditt val.

SCB-koder*

3. Medicin och hälsovetenskap > 302. Klinisk medicin > 30215. Psykiatri

Ange minst tre och upp till fem kortfattade nyckelord som beskriver projektet.

Nyckelord 1*

Depression

Nyckelord 2*

Anxiety

Nyckelord 3*

Premenstrual dysphoric disorder

Nyckelord 4

Serotonin

Nyckelord 5

Antidepressants

Etiska överväganden

Redovisa tydligt de etiska frågor som projektet (eller motsvarande) aktualiserar och redogör för hur de behandlas i forskningsarbetet. Markera också de specifika aspekter som eventuellt berör din ansökan.

Redogörelse för etiska överväganden*

I studierna baserade på databaser, som t ex post hoc-analyserna av SSRI-studier och samarbetet med LifeGene-konsortiet, har vi enbart tillgång till avidentifierade data, varför projektet inte innebär något äventyrande av deltagarnas integritet. De kliniska projekten är eller kommer att bli godkända av den regionala etikprövningsnämnden och är ej förenade med något större obehag eller några risker för deltagarna. De djurexperimentella studierna är godkända eller kommer att godkännas av forskningsetisk kommitté.

I projektet ingår hantering av persondata

Ja

I projektet ingår djurförsök

Ja

I projektet ingår humanförsök

Ja

Forskningsplan

Bifoga din forskningsplan i PDF-format i enlighet med instruktionerna i utlysningstexten.

Du kan endast bifoga en fil och den får maximalt vara 10 MB stor. Klicka först på mappsymbolen för att söka fram filen på hårddisk, klicka sedan på plustecknet för att ladda upp filen i formuläret.

Forskningsplan*

Se nästa sida för bilaga.

E Eriksson: SELECTIVE SEROTONIN REUPTAKE INHIBITORS: CONTROVERSIES AND ENIGMAS

Purpose and aims

Used for depression and a variety of other psychiatric conditions by 7% of the population, the selective serotonin reuptake inhibitors (SSRIs) remain highly controversial. 25 years after they were introduced there is hence still no consensus regarding the pivotal question if they actually exert any antidepressant effect.

After having conducted trial-based meta-analyses on all placebo-controlled trials once conducted by the drug companies to establish the antidepressant effect of these drugs, influential debaters have thus came to the conclusion that the SSRIs are at best marginally more effective than placebo, and that this superiority is not a specific pharmacological effect, but the result of an enhanced psychological placebo phenomenon elicited by side effects making the patient realize that he/she has not been allotted placebo (1,2).

Given the gravity of the disorders for which they are used, and since there are no reasons to assume that any novel treatment will emerge in a foreseeable future that will render the SSRIs redundant, it is a task of the utmost importance to settle the current controversy regarding the efficacy, or lack of efficacy, of these medications. One aim of this project hence is to address the alleged ineffectiveness of these drugs.

Even among researchers believing the SSRIs to be effective, most would probably agree that our knowledge on their mechanism of action remains disturbingly poor. Thus, while there is little doubt that the serotonin transporter indeed is their primary molecular target, it remains (for example) unclear

i) why they display a sluggish onset of action when used for some conditions (such as depression and anxiety disorders) but not for others (such as premenstrual dyshporia),

ii) if their net influence on serotonin output (at acute and continuous administration, respectively) is best described as facilitating or dampening,

iii) how their various therapeutic effects relate to the physiological influence of brain serotonergic transmission on behavior, and

iv) which of the many different serotonin receptor subtypes that mediate the wanted and unwanted effects of these drugs.

The aims of this project hence are twofold: *Project A)* By conducting post hoc analyses of a unique data bank comprising patient level-data from most drug company-sponsored placebo-controlled SSRI trials ever conducted we hope to resolve the issue of their alleged ineffectiveness and other related questions. *Project B)* By means of a combination of animal and clinical experiments we hope to enhance the understanding of the mechanism of action of the SSRIs, and of how the clinical effects of these substances may relate to the physiological role of brain serotonin.

Project A: Post hoc analysis assessing the alleged ineffectiveness of SSRIs

Survey of the field

A pharmaceutical company gaining marketing authorization by FDA or EMA for a novel antidepressant traditionally has hinged on to what extent the company has been able to show the drug to be superior to placebo in at least two controlled trials. The fact that all

SSRI producers have also undertaken trials failing to demonstrate efficacy of the tested drug – trials that have seldom been published – have hence not preclude approval.

In recent years, the fact that >50% of all SSRI versus placebo trials were in fact negative however has led to a questioning of the efficacy of these drugs. On the basis of trial-based meta-analyses comprising both negative and positive trials, widely cited researchers, such as Irving Kirsch at Harvard, have thus concluded that the difference between placebo and SSRI is in fact too small to be clinically meaningful, and unlikely to be due to a specific pharmacodynamic effect of the drug; instead Kirsch suggests that an SSRI sometimes outperforming placebo is caused by side effects making patients getting the active drug believing that they have received an active medication and experiencing an enhanced placebo response for this reason ("extra strength placebo") (1,2).

The current questioning of the efficacy of the SSRIs have had a marked impact on opinion leaders and been widely disseminated in public media. For example, the former editor-in-chief of New England Journal of Medicine, Marcia Angell, who is professor at Harvard, has provided strong support for the view of Dr Kirsch, questioning if drugs used in psychiatry, including the SSRIs, are of any value (3). In the same vein, professor Peter Gœtsche at Rigshospitalet in Coenhagen, and head of the Danish Cochrane Institute, has claimed that it would be an advantage if all psychoactive drugs were removed from the market (4). Also, on the editorial page of Sweden's largest newspaper, Dagens Nyheter, a columnist, referring to the study by Kirsch, recently described psychiatry as "a branch of hustlers and swindlers" (5).

Even more importantly, the current debate has influenced official bodies producing treatment recommendations; in a CBS broadcast ("60 minutes") a spokesperson for the National Institute of Clinical Excellence (NICE) thus claimed that antidepressants are "not worth having" for mild or moderate depression (6). In the same vein, the Swedish Board of Health and Welfare in their most recent guidelines found no support for antidepressant being superior to a novel and yet very poorly evaluated treatment, internet-based CBT, for this group (and found the latter treatment being more cost-effective) (7).

Another concern that has markedly dampened the enthusiasm for the SSRIs is that that they, according to some, including UK psychiatrist David Healy, may provoke suicide in patients without suicidal ideation before treatment (8). Data from placebo-controlled trials suggesting suicidal ideation (but not suicide) being more common in children given SSRI thus prompted authorities in many countries to issue a *black box warning* regarding the use of these compounds for depression in the young (9). On the other hand, others have pointed out that the increase in the use of antidepressants during the past decades has coincided with a marked reduction in suicide, the net effect of SSRI on suicide hence remaining a highly controversial issue (10).

An effective treatment should indeed be expected to outperform placebo in a vast majority of sufficiently sized trials; the high rate of unsuccessful SSRI studies hence is a matter of legitimate concern, as are the reports that SSRIs may enhance suicidal ideation. If antidepressants exert no beneficial effect, but a suicide-provoking action, their current use should be reconsidered, as should investments into research based on the assumption that they do exert a specific, transmitter-related action.

On the other hand, if the questioning of the efficacy of these drugs is unfounded, the claim that they are useless may cause harm by making doctors refrain from prescribing an effective medication. The current situation, where these drugs are used by 7% of the

population, but at the same time described as more or less ineffective by many debaters, including representatives of bodies such as NICE, clearly is highly dissatisfying.

There are no reasons to believe that novel drugs replacing the SSRIs as pharmacological first line of treatment of depression and anxiety will be introduced within a foreseeable future. Also, given that all SSRIs are now off patent, it seems highly unlikely that anyone would be able to fund the large new placebo-controlled trials that would be required to settle the current controversies regarding these drugs.

To only available strategy to shed light on this issue hence seems to be to re-analyze the trials that have been the impetus for the current questioning of the usefulness of the SSRIs. The aim of project A hence is to analyze why many SSRI trials are negative while others are not, i.e. if the negative trials reflect a true inability of SSRIs to generate an antidepressant signal, or if the frequent failures to demonstrate a beneficial effect may be caused by methodological problems. Other related issue, such as the alleged suicide-provoking effect of these drugs, will be addressed as well.

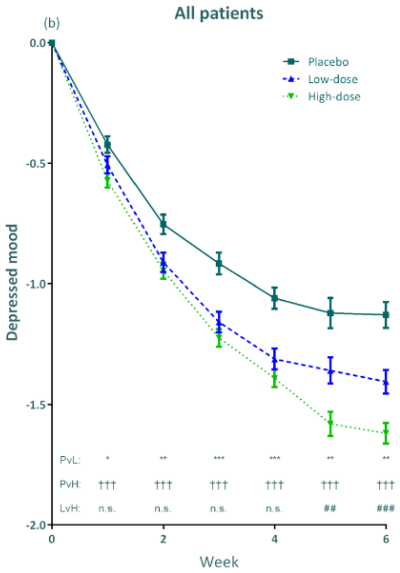
Project description

General design, logistics, methods: While most post hoc analyses of past antidepressant trials have been trial-level meta-analyses, which are marred by numerous methodological shortcomings (11), our approach is different in the sense that we base our post-hoc calculations on patient-level rather than trial-level data. Such an approach has until now been uncommon, and, when undertaken, only comprised a small number of trials, one important reason probably being that the pharmaceutical companies have usually regarded patient-level data as confidential information and hence been reluctant to share them with independent researchers. After a few years of negotiations, we have however now obtained patient-level data from all placebo-controlled trials in adult depressed patients performed by Pfizer, GSK and Lundbeck regarding three of the four first generation SSRIs, i.e. sertraline, paroxetine and citalopram; this data bank includes information from 32 different SSRI-placebo comparisons in total comprising 6669 patients. In addition, we have good reasons to believe that we will shortly have access to corresponding data also from studies in children and adolescents and for other SSRI indications than depression.

One PhD student, F Hieronymus, is working full time on this project and it will involve other PhD students as well. Whereas the data have been obtained from pharmaceutical companies, these are in no other any way involved in the project. We are working in close collaboration with statistical expertise (S Nilsson, Chalmers, Gothenburg).

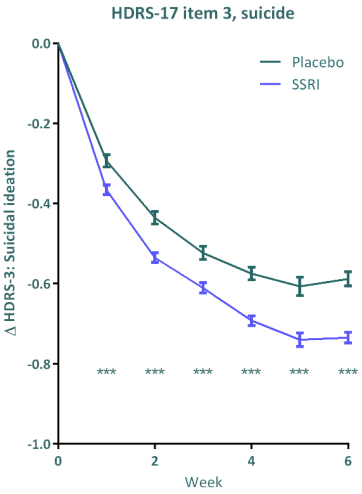
Issues (1): The importance of choice of effect parameter for outcome: For the majority of antidepressant drug trials, the decrease in the total score of the 17 different items included in the Hamilton depression rating scale (HDRS) has served as primary effect parameter. Constructed in the late 50s, this multidimensional scale is however marred by numerous shortcomings that might be expected to reduce its ability to pick up an antidepressant signal (11). To explore if the use of this measure may partly explain why many SSRI trials have been negative, we re-analyzed thirty-two different SSRI vs placebo comparisons after replacing the HDRS17-sum as effect parameter with a single item that, unlike many of the other items, is reported by a vast majority of the participants at baseline, i.e. depressed mood. The outcome of this analysis was more striking than we had expected. Thus, while 18 out of 32 comparisons (56%) failed to separate active drug from placebo when using the conventional primary effect parameter, i.e. the HDRS17-sum, only 9% of the comparisons were negative when depressed mood was used as effect parameter (12). We thus suggest

that the negative outcome of many placebo-controlled SSRI trials may be regarded as an artifact caused by the use of a suboptimal rating scale. Indeed, an antidepressant signal being detected in almost all trials suggests the beneficial effect of these drugs, in contrast to conventional wisdom, to be very robust and reproducible across trials.



Issues (2): The matter of dose-response: It is often claimed that it has never been possible to establish clear-cut dose-response relationships for the SSRIs, and this has constituted an important argument for those questioning the existence of a specific antidepressant effect. Using a pooled population of a large number of fixed-dose SSRI versus placebo trials (number of patients = 2895), and the item depressed mood as effect parameter, we have however been able to detect a clear dose-response response relationship. Further analyses will enable us to provide guidance regarding the association between dose and response for each of the studied SSRIs. This work is in progress.

Issues (3): The "side effect breaking the blind" hypothesis: It has since long been suggested that the side effects of active treatment may break the blind for both the patient and the investigator in controlled trials, and recently Kirsch and co-workers have gained wide popularity for the theory that this phenomenon may underlie the superiority of SSRIs over placebo sometimes observed (1,2). Shortly we will be able to test this hypothesis for most SSRIs by exploring the possible association between side effect and response. As yet we have however completed such an analysis for escitalopram only; these preliminary data are however of considerable interest in the sense that they suggest that presence of side effects do not at all influence the difference between active drug and placebo. In case similar results will be obtained also with other antidepressants, the "side effect breaking the blind" hypothesis" may be regarded as definitely refuted.



Issue (4): Suicide-provoking effect of SSRIs?: A possible initial suicide-provoking effect of SSRIs was assessed by analyzing the suicide item in the HDRS in a pooled population comprising all company-sponsored trials using paroxetine, sertraline or citalopram (n>8000). As shown, no sign of a suicidogenic effect was detected even during the first weeks of treatment; in contrast, a significant difference in the opposite direction was observed already at week 1. Future analyses on this issue will consider also self-reported side effects and early drop-outs.

Issues (5): SSRI effects in children: All the SSRI versus placebo comparisons described above will be conducted also in studies of SSRI treatment in children and adolescence. This work is in the planning phase.

Issues (6): Comparison of SSRIs with tricyclic antidepressants: Patient level-based post hoc analyses will also be undertaken to address the possible difference between different classes of antidepressants along the same line as the studies presented above, i.e. using

depressed mood as primary effect parameter, our a priori hypothesis being that certain tricylic drugs, such as amitriptyline and clomipramine, will turn out to displayer larger antidepressant effect than the SSRIs. As yet no data from such analyses are available.

Issues (7): Predictors of response: Whereas the aim of our post hoc analyses of placebo-controlled SSRI trials has hitherto mainly been to address some outstanding controversies regarding the efficacy and safety of these drugs, we are confident that out unique data bank of patient-level data from SSRI trials will be highly informative also for the purpose of exploring possible predictors of response to active drug and placebo, respectively, such as age, gender, severity and symptom profile. As yet no data from such analyses are available.

Work plan: Whereas our report on the effects of replacing HDRS17-sum with depressed mood as effect parameter is in press, analyses of the other issues mentioned above are ongoing and will be continued next year when we will also address the same aspects in studies on children and adolescents. In 2017, we plan to explore *i)* possible predictors for response in different age groups, *ii)* the relative efficacy of different classes of antidepressant drugs and *iii)* SSRI efficacy in conditions other than depression.

Significance

We believe that various aspects of our approach – our focus on patient level data, the very large number of trials included in our data bank and our replacing HDRS17-sum with a more sensitive outcome parameter – makes it uniquely apt to resolve many of the outstanding controversies regarding the usefulness of SSRIs; it hence does not appear unlikely that the outcome of our analyses will influence future treatment guidelines worldwide. Also, we hope that our observations will foster an improved design of depression trials.

Supporting that our results will indeed be received with some interest by the psychiatric scientific community, the first paper from this study was recently accepted for publication in *Molecular Psychiatry* which is currently ranked as number 1 among the psychiatric journals (impact factor: 15); moreover, even before this report has been published, the applicant has been invited to several international meetings (CINP, IFMAD, DPPGN and SCNP) to discuss these issues, and to debate them with researchers advocating an alternative view (such as the above-mentioned Drs Kirsch and Healy).

Preliminary results

For enhanced clarity, the preliminary results have been presented above.

Project B: Combined preclinical and clinical studies addressing the mechanism of action of SSRIs

Survey of the field

While project A aims at clarifying the pros and cons of the SSRIs in the clinical setting, project B aims at shedding further light on *why* these drugs are effective in conditions as disparate as depression, panic disorder and premenstrual dysphoric disorder.

Early studies from our group led to the introduction of a strong serotonin reuptake inhibitor, clomipramine, for the treatment of panic disorder in Europe; this was the first time ever an antidepressant was approved for this indication (13) where SSRIs are now first line of treatment worldwide. While we were duly impressed by the very high rate of clomipramine-treated patients reporting complete disappearance of panic attacks after 12

weeks of treatment, we were also struck by the fact (which is now widely recognized) that a majority of panic disorder patients experience markedly *enhanced* anxiety during the first days of treatment.

Later we were the first to report that a severe variant of premenstrual syndrome, premenstrual dysphoric disorder (PMDD), respond with a remarkable effect size and response rate to SSRIs, and also that this effect, unlike the antidepressant and anti-anxiety effects, is fully developed already shortly after onset of treatment (for refs see 14,15,16,17). These observations have had a considerable impact on the clinical management of this common condition – intermittent SSRI administration (from ovulation to the onset of menstruation) is hence now regarded as first line of treatment worldwide and the only approved treatment of PMDD in Sweden. They were, in our view, however also of considerable theoretical interest since they, for the first time, demonstrated that beneficial, symptom-reducing effects of SSRIs may indeed be observed much earlier (=within hours) (17) than previously assumed.

We thus found it interesting that acute administration of SSRIs may exert both an acute anxiety-provoking effect (observed mainly but not exclusively in panic disorder patients) and an acute irritability-reducing effect (first observed in patients with PMDD but subsequently also in other conditions characterized by anger and hostility). We also found it noteworthy that two of the side effects of SSRIs, i.e. nausea and a reduction in sexual interest, also appear already shortly after onset of treatment.

What makes this constellation of effects observed shortly after the onset of SSRI administration particularly intriguing is that they are in perfect consonance with the behavioural effects observed in experimental animals after serotonin depletion; the most obvious consequences of such an intervention hence are *reduced* anxiety (as assessed using various animal models of anxiety, such as the elevated plus maze), *enhanced* sexual activity, *enhanced* aggression and *enhanced* food intake.

Taken together, these findings suggest that serotonin, in both rodent and man, serves to *enhance* anxiety and to *dampen* sexual activity, aggression and food intake. From an evolutionary point of view, it may be speculated that serotonin has served as a transmitter modulating our propensity to shift attention, in the presence of a threat, *from* activities such as food intake, sex and aggression, *to* fear and flight. According to this theory, subjects with high serotonergic activity would hence be characterized by high inclination for anxiety but low inclination for, e.g., aggression, and vice versa.

Traditionally the SSRIs have been assumed to enhance serotonergic output at long-term administration, such an increase being their presumed mechanism of action when used for the treatment of anxiety disorders (including panic disorder) and depression. If one regards serotonin as mainly an anxiogenic transmitter (see above), a more likely explanation to the beneficial effects of SSRIs upon continuous administration would however be that they exert a gradual adaptive down-regulation of an anxiogenic serotonergic influence. We have recently observed support for this assumption (see below).

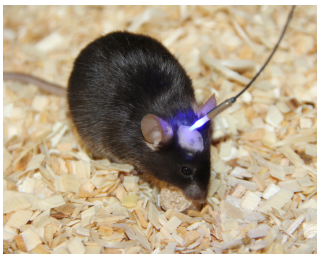
Another aspect of interest in this context is the apparent association between serotonergic transmission and sex steroids, two of the most striking effects of serotonin depletion in animals being an increase in two sex steroid-driven aspects of behavior: sex and aggression. It is also noteworthy that PMDD, which is a sex steroid-dependent condition, is the SSRI indication displaying the largest effect size and response rate, and that reduced

libido is the most prevalent side effect of these drugs. A physiological key role of serotonin hence seems to be to dampen sex steroid-driven behavior.

The aims of project B, which is based on preclinical and clinical studies combined, are *i)* to explore the above-mentioned hypothesis regarding the possible role of changes in serotonergic output for the short- and long-term behavioural effects of the SSRIs, *ii)* to identify the postsynaptic receptors mediating the various behavioural effects of the SSRIs, and especially the anxiogenic effect observed after acute administration, and *iii)* to shed further light on the interplay between serotonin and sex steroids for the regulation of behavior, and for male-female differences in this regard.

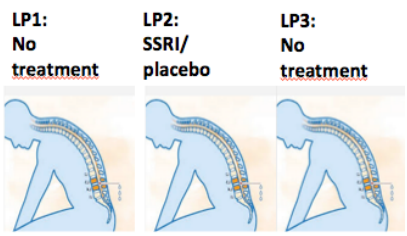
Project description

General design, logistics, methods: For our animal experiments, which are undertaken in both rats and mice, we apply the following tentative animal models of anxiety: elevated plus maze, light-dark box test, open field test, and conditioned and non-conditioned startle and freezing. For assessment of aggression, the resident intruder test is applied. Sexual behavior (lordosis, mounting) and motivation (time spent in the vicinity of an animal of the opposite sex) are assessed in both male and female rodents. Serotonin activity is measured using assessment of *i)* the expression of serotonin-related genes (low density array), *ii)* levels of serotonin-related proteins measured by means of Western Blot and *iii)* concentrations of serotonin and its metabolite (5-HIAA) in brain homogenate (ex vivo) and in samples of extracellular fluid obtained using in vivo micro-dialysis. As a sign of enhanced neuronal activity following various treatments, expression of the immediate early gene fos in various brain regions is assessed using immunohistochemistry. Serotonin activity is modulated using pharmacological tools, such as SSRIs (given acutely or chronically), the serotonin synthesis inhibitor pCPA and various serotonin receptor agonists and antagonists, and also by means of genetic modulation (including mice unable to express the serotonin synthesizing enzyme, TPH2).



Recently we have also established a method at our lab whereby light reactive proteins (opsins) are expressed in specific subtypes of mammalian neurons to allow precise temporal control of their firing, i.e. optogenetics (18). To this end, we use transgenic mice that express channelrhodopsin (an opsin that activates neurons) selectively in serotonergic neurons to enhance serotonergic firing; as a first proof of the feasibility of this technique in our hands, preliminary data from our laboratory show an anti-aggressive effect of such an activation of serotonergic output. To silence serotonergic neurons, we use viral vectors to express opsins in discrete brain regions of rats or mice. The optogenetic studies are carried out by post doc Alana Knapman who has learnt the technique at the lab of its inventor, Kars Deisseroth at Stanford.

Parallel clinical studies are undertaken to explore acute effects of SSRIs on relevant biomarkers in blood and cerebrospinal fluid using modern analytical techniques (including ultra-sensitive HPLC and ELISA, RIA, LC-MS/MS and mass spectrometry). A unique feature of these studies is that we have established a well-functioning routine by means of which CSF samples are obtained at three different occasions, with no treatment at sampling 1 and 3 and with administration of SSRI or placebo at



sampling 2; unlike almost all previous studies in the field, this project will hence provide us with information not only regarding possible effects of the SSRI administration but also regarding the intra-individual inter-test stability of the studied biomarkers. In addition, most previous studies analysing the effect of SSRIs on CSF markers (which are not many) were conducted decades ago when the analytical techniques were far less sophisticated and sensitive than today. We hence believe that there are good chances that our approach will reveal new and important knowledge both regarding the inter-test stability of the studied biomarkers (and the possible interplay between them), and with respect to how these are influenced by acute SSRI administration. A first study, including 30 healthy volunteers, has been concluded; the CSF samples now (March 2015) being the subject of analysis, partly in collaboration with Drs Blennow and Zetterberg at Sahlgrenska. A new study, that will comprise women with premenstrual dysphoria assessed once in the follicular phase and twice in the luteal phase (when on placebo or SSSRI) is shortly to be started.

Issue (1): Using anxious Wistar rats to study the anxiogenic influence of serotonin: While serotonin depletion (obtained e.g. by administration of the serotonin synthesis inhibitor p-CPA) reliably reduces anxiety as assessed using the elevated plus maze (both in our hands and those of others), the literature regarding a possible anxiogenic effect of an SSRI in rodents (corresponding to the anxiogenic effect observed after acute administration of an SSRI in humans, such as patients with panic disorder) is far from unanimous. Recently, we however observed a marked association between baseline anxiety and acute response to an SSRI in a batch of outbred Wistar rats: while rats displaying high anxiety at baseline displayed a further enhancement of anxiety following the administration of an SSRI, no corresponding effect was seen in non-anxious animals (19).

Supporting the hypothesis that inter-individual differences with respect to an anxiogenic influence of serotonin may underlie inter-individual differences in anxiety in rat, we also found animals with high anxiety at baseline to display indices of enhanced serotonergic transmission (such as enhanced TPH2 expression in the raphe region); moreover, pCPA-induced serotonin depletion reduced anxiety in anxious but not in non-anxious animals hence abolishing the difference between the two groups. In addition, we found subchronic administration of an SSRI to blunt the anxiogenic effect of acute SSRI administration in anxious animals (19). Finally, the observation that animals displaying elevated anxiety at baseline are more inclined to respond with enhanced anxiety to an SSRI was replicated in another experiment, using a different model of anxiety, i.e. fear-potentiated startle (20).

We find these recent observations important for several reasons. First, they support our hypothesis that inter-individual differences in anxiety may be related to inter-individual differences in an anxiogenic influence of serotonin, and that the anxiety-reducing effect of chronic SSRI administration is the result of a down-regulation rather than an augmentation of serotonergic output. And second, they have made us realize that selecting animals displaying high anxiety at baseline, rather than assuming all rats in a batch to be identical, will largely enhance our possibilities to further explore the mechanisms underlying the anxiogenic effect of SSRIs in susceptible individuals.

In ongoing and planned studies, we will use SSRI-induced anxiety (reflected by elevated plus maze or fear-potentiated startle) in an attempt to shed further light on the anxiogenic influence of serotonin in general and the phenomenon of SSRI-induced anxiety in particular, e.g. with respect to the involvement of specific serotonin receptor subtypes. Recent experiments in our laboratory suggesting SSRI-induced anxiety to be blocked by 5-

HT6 but not by 5-HT2C antagonists (Näslund et al, unpublished) will be followed up by experiments addressing the possible involvement of all known serotonin receptor subtypes. In an attempt to localize the anxiogenic effect of SSRIs, animals with low and high baseline anxiety are compared with respect to fos expression following SSRI administration. We will also examine to what extent activation of different populations of serotonin neurons by means of optogenetics will induce anxiety preferentially in rats with high baseline anxiety, the effect of such effects on fos expression, and the possibility to block it using various 5-HT receptor antagonists. Finally, we will examine to what extent chronic SSRI administration induces changes in the expression of serotonin-related genes in various terminal regions in a way that may shed light on the reduced responsiveness to acute SSRI administration displayed by anxious Wistar rats given such treatment.

Issue (2): Studies on the interaction of serotonin, dopamine and sex steroids for the regulation of anxiety, sex and aggression: The striking antagonism exerted by serotonin and testosterone with respect to the regulation of various aspects of behavior (anxiety being enhanced by serotonin and reduced by testosterone, and sexual activity and aggression both being reduced by serotonin and enhanced by testosterone) have made us explore the possibility that testosterone exerts its behavioural effects by inhibiting serotonergic transmission. These experiments show, e.g., that serotonin depletion cannot restore aggression in gonadctomized males (21), but, on the other hand, that serotonin depletion does reduce gonadectomy-induced anxiety (Näslund et al, prel ms 2015). Supporting our hypothesis that serotonin is important for upholding sex differences in behavior, we have shown serotonin depletion to eliminate such differences both with respect to the elevated plus maze and fear-potentiated freezing (22,23). In ongoing and future experiments, optogenetic-induced modulation of serotonergic activity will be used to shed further light on the interactions between serotonin and sex steroids.

Issue (3): Effects of SSRIs on CSF biomarkers in humans: For long, the serotonin levels in CSF have been regarded too low to measure: hence the pivotal (and controversial) issue of to what extent acute SSRI administration indeed enhances extracellular serotonin in humans remain unanswered. By using modern techniques (HPLC, mass spectrometry or ELISA), we however hope to be able to measure CSF amines (and not merely their metabolites), which means that we will, for the first time, be able to answer this question. Our clinical studies based on repeated CSF sampling in healthy volunteers when untreated or when on SSRI/placebo (where the sampling has now been completed) will also enable us to address numerous other issues: the degree of inter-test stability of a variety of relevant transmission-related aminergic and peptidergic biomarkers, the possible correlation between dopamine and serotonin (and other relevant biomarkers), the possible correlation between sex steroids and metabolites thereof (such as allopregnanolone) and monoamines, the possible correlation between the neurotrophic factor BDNF and monoamines, and the possible acute effects of SSRI on these and other parameters. In a forthcoming study including women with or without PMDD that will also be the subject of repeated CSF sampling (in one follicular and two luteal phases, with or without the presence of an SSRI) we will also be able to explore the influence of cycle phase on these parameters.

Work plan: The above-mentioned animal experiments will last for 2-3 years and involve at least two PhD students (Robert Pettersson and Melker Hagsäter) and one post doc (Alana Knapman). The analyses of samples from the now completed human study will be undertaken during 2015 and 2016. The PMDD study will start during fall 2016 and go on

for 1.5 years and involve at least one PhD student, psychiatrist Johan Fredrik Emilsson.

Significance

As discussed above, we believe that we are approaching an enhanced understanding of the relationship between the clinical effects exerted by SSRIs at acute and chronic administration on the one hand, and the physiological influence exerted by serotonin on behavior on the other. Our attempts to identify the receptor subtypes involved in the various behavioral effects of SSRIs may tentatively facilitate the development of new and better drugs.

Preliminary findings

Two PhD students (Jakob Näslund and Erik Studer) will defend their theses in June 2015 and have submitted or will submit in total 8 papers during early spring 2015. For clarity, some of these results have been discussed above; for brevity, some of them are not discussed in this document (but mentioned in the scientific report).

The first result from the CSF study discussed above, which was recently published in Science Translational Medicine (impact: 14), unfortunately was a negative one; we were hence unable to replicate the result from another group that short term administration of an SSRI reduces CSF levels of various markers for Alzheimer's disease.

For brevity, recent results from an ongoing epidemiological study that sheds new light on the definition of premenstrual dysphoric disorder, conducted in collaboration with the LifeGene consortium, will not be described here but is mentioned in the scientific report. Likewise, for a description of our recent data showing, for the first time, that a dopamine stabilizer exerts marked anti-aggressive effects in rodents, at doses not affecting locomotion, other aspect of social behavior or sexual behavior, we also refer to the scientific report. Both these project will be pursued further during the forthcoming years.

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Tvärvetenskap

Min ansökan är tvärvetenskaplig

☐

Ett tvärvetenskapligt forskningsprojekt definieras i denna utlysning som att det för sitt genomförande behöver sakkunskaper, metoder, terminologi, data samt forskare från fler än ett av Vetenskapsrådets ämnesområden medicin och hälsa, naturvetenskap och teknikvetenskap, humaniora och samhällsvetenskap samt utbildningsvetenskap. Om ditt forskningsprojekt är tvärvetenskapligt enligt denna definition anger och redogör du för detta här.

Klicka här för vidare instruktioner

Särskild satsning

Särskild satsning

Psykiatri

Projektet omfattar kliniska och djurexperimentella studier med syfte att belysa användandet av selektiva serotoninåterupptagshämmare vid ett antal psykiatriska tillstånd. Projektet har härmed, i alla sina delar, en tydlig psykiatrisk inriktning.

Vetenskaplig rapport

Vetenskaplig rapport/redogörelse för vetenskaplig verksamhet inom tidigare projekt

Project: How do the serotonin reuptake inhibitors exert their effects?

Amount: SEK 2,100,000

Grant number: 2012-5665

During the grant period (i.e. from 2013 an onwards), the project has resulted in 19 publications that are published or in press including original papers, review articles and letters; some of these have appeared (or will appear) in journals with impact factor >10: one original article in Mol Psych (IF: 15), one original article in Science Translational Medicine (comment with original data) (IF: 14), one review in American Journal of Psychiatry (IF: 14) and one short letter (debate) in Lancet (IF: 39). Two PhD students (Erik Studer and Jakob Näslund) are to defend their theses in June 2015; in total these theses will comprise 11 papers, 8 of which have been submitted or will be submitted during the period January-March 2015; these are hence not yet accepted for publication and therefore not included in the enclosed list of publications (or included in the numbers provided above). Both these theses will mainly (but not solely) include papers based on preclinical studies.

Since recent and preliminary data are to some extent reported in the research program, only some of our recent achievements will be mentioned here:

1. By utilizing the fact that there are clear-cut and stable inter-individual differences in anxiety within a batch of outbred Wistar rats, we have obtained support for the assumption that inter-individual differences in anxiety are partly due to inter-individual differences in an anxiogenic influence of serotonin. This observation has also enabled further studies on how this influence is organized that would have been difficult to pursue had we not realized that we should take baseline anxiety into consideration. We hence believe the results presented in our recent paper on this issue (Näslund et al, Int J Neuropsychopharmacology, epub ahead of print; IF=5) to be of considerable importance for our future studies. In more recent experiments, we have found the anxiogenic effect of SSRI in anxious animals to be antagonized by a 5-HT6 receptor-blocking agent (Näslund et al, prel ms 2015A). An association between baseline anxiety and response to an SSRI has been observed also using another tentative animal model of anxiety (Pettersson et al, Psychopharmacology, IF=4).

2. In several studies, such as the one mentioned above, we have found assessment of the expression of a large number of serotonin-related genes to provide valuable insight into the status of the serotonergic activity in rats; yet, it should be realized that it is far from clarified how gene expression data should be interpreted, and how responsive gene expression is to various stimuli. To this end, we have recently completed a study examining the influence of marked but short-term changes in extracellular serotonin concentrations on the expression of serotonin-related genes, observing some genes in some areas to display marked changes in expression while others remain unaffected (Näslund et al, prel ms 2015B). Gene expression studies have also provided interesting insight into the interaction between sex steroids and brain serotonergic neurotransmission; thus, strong correlations between sex steroid-related genes and serotonin-related genes, which often disappear after gonadectomy, were found in many brain areas (Studer et al, prel ms, 2015A). A study of the expression of the gene encoding the serotonin syntehsizing enzyme TPH2 in males and females revealed differences between the sexes and, in females, between the different phases of the estrous cycle (Studer et al, prel ms, 2015B).

3. We are intrigued by our finding that sex differences in two different animal models of anxiety are abolished by serotonin depletion (Näslund et al, Psychopharmacology, 230:29-35, 2013, IF=4; Pettersson et al, submitted ms, 2015) since these results are in line with our hypothesis that serotonin serves to uphold certain sex differences in behavior. Of interest is also the observation that the increase in anxiety observed in non-anxious male rats following gonadectomy may be reversed by serotonin depletion (Näslund et al, prel ms 2015B). In contrast, we have shown that serotonin depletion can not restore aggression in male mice rendered non-aggressive by means of gonadectomy or androgen receptor knockout (Studer et al, PLOS One, IF=3.5; in press, 2015); the anti-aggressive effect of serotonin hence seem to require the presence of androgens to be at hand.

4. Developed by the 2000 Nobel laureate Arvid Carlsson, OSU6162 is a so-called dopamine stabilizer, i.e. a compound that reduces locomotion in active animals and stimulates it in those with low activity, the tentative mechanism of action being selective antagonism of extra-synaptic D2 receptors. Together with Carlsson, we have now found OSU6162, at does influencing neither locomotion nor sexual activity, to exert a marked anti-aggressive effect in male mice; in addition, it displayed activity in a tentative aggression-based animal model of premenstrual dysphoria previously developed by us (Studer et al, submitted ms 2015A). We suggest that OSU6162 may prove useful for the treatment of premenstrual dysphoria as well as other conditions characterized by anger or irritability.

5. We find it deeply satisfying that we, thanks to the effort of post doc Alana Knapman, who got her training in the technique at the Deisseroth laboratory at Stanford (where it was developed), have been able to set up optogenetics as a novel assett for our studies on the regulation and impact of brain serotonergic neurons. The observation that optogentic stimulation of serotonergic neurons in raphe reduces aggression in male mice is novel (though in line with previous pharmacological data) and will shortly be published.

6. Prompted by our interest in PMDD, not least as an atypical SSRI indication (see above and research program), we have recently conducted (in collaboration with the LifeGene consortium) a study in which >10000 women of fertile age were exposed to a web questionnaire regarding possible premenstrual symptoms. The study, that is the largest undertaken regarding this condition so far, and in various aspects unique, provided support for the notion that irritability and affect lability are by far the most common and most impairing symptoms, and that some complaints often attributed importance in this context, and listed among the DSM criteria for this coindition, are in fact so rare that their relevance may be questioned (Studer et al, submitted ms 2015B).

7. Our clinical study in which repeated sampling of cerebrospinal fluid was obtained from healthy controls before, during and after administration of an SSRI (escitalopram) or placebo has been successfully concluded, the samples now being the subject of various analyses. Since complications of the repeated lumbar punctures, such as headache, were rare and mild, we now plan to conduct a similar study comprising women with premenstrual dysphoria that will be studied in different phases of the menstrual cycle (and when treated with an SSRI or placebo) (see research program).

8. Preliminary data from the project based on post hoc analyses of patient-level data from placebo-controlled SSRI trials in adult depression are presented in the research program and will hence not be commented further here. As yet, this project has resulted in one paper only (Hieroynmus et al, Mol Psychiatry, in press 2015; IF:15), but additional manuscripts will be submitted shortly.

Resources:

Apart from our VR grant, we have received ALF funding for tha past 3 years to an amount of SEK 5 million; this funding will however be considerably lower for the fortcoming 3 year period. In December 2014, we received a VR grant dedicated to "clinical treatment studies" of SEK 11 million; this grant will however be spent on a study of a novel treatment for Parkinson's disease and can not be used for the project presented in the present application.

Budget och forskningsresurser

Personal i projektet

Redovisa vilken personal som ska arbeta i projektet och lönekostnaderna för dessa som du ansöker om från Vetenskapsrådet. Ange hela beloppet, ej i tusental kronor.

Medverkande forskare som accepterar inbjudan att delta i ansökan visas automatiskt under Aktivitetsgrad. Observera att det kan ta några minuter innan informationen uppdateras och det kan krävas att projektledaren stänger och sen öppnar formuläret på nytt.

Aktivitetsgrad i projektet

	Roll i projektet	Namn	Procent av heltid
1	Projektledare	Elias Eriksson	

Löner inklusive sociala avgifter

	Roll i projektet	Namn	Procent av lönen	2016	2017	2018	2019	2020	Totalt
1	Övrig ej disputerad personal	Gunilla Bourghardt	100	560 000	560 000	560 000	560 000	560 000	2 800 000
2	Övrig ej disputerad personal	Fredrik Hieroynymus	100	550 000	550 000	550 000	550 000	550 000	2 750 000
	Totalt			1 110 000	1 110 000	1 110 000	1 110 000	1 110 000	5 550 000

Övriga kostnader

Ange övriga kostnader i projektet som du ansöker om från Vetenskapsrådet. Ange hela beloppet, ej i tusental kronor.

Lokaler

Typ av lokal	2016	2017	2018	2019	2020

Driftskostnader

	Driftskostnader	Beskrivning	2016	2017	2018	2019	2020	Totalt
1	Försöksdjur etc		300 000	300 000	300 000	300 000	300 000	1 500 000
2	Kostnader klinisk studie		500 000	500 000	500 000	500 000	500 000	2 500 000
3	Datorer, resor, litteratur etc		100 000	100 000	100 000	100 000	100 000	500 000
4	Lab-kostnader		300 000	300 000	300 000	300 000	300 000	1 500 000
	Totalt		1 200 000	1 200 000	1 200 000	1 200 000	1 200 000	6 000 000

Avskrivningar utrustning

Avskrivning	Beskrivning	2016	2017	2018	2019	2020

Total kostnad för projektet

Nedan summeras de kostnader som du har fört in i din budget och därmed ansöker om från Vetenskapsrådet. Indirekta kostnader för du in separat i tabellen.

Under Annan kostnad anger du eventuella ytterligare kostnader, utöver det du ansöker om från Vetenskapsrådet, som genomförandet av projektet medför. Ange hela beloppet, ej i tusental kronor.

Delsumma plus indirekta kostnader per år utgör sökt belopp från Vetenskapsrådet.

Total kostnad för projektet

Specificerade ko..	2016	2017	2018	2019	2020	Totalt, sökt	Annan kostnad	Total kostnad
Löner inkl. sociala avgifter	1 110 000	1 110 000	1 110 000	1 110 000	1 110 000	5 550 000		5 550 000
Driftskostnader	1 200 000	1 200 000	1 200 000	1 200 000	1 200 000	6 000 000		6 000 000
Avskrivningar utrustning						0		0
Lokaler						0		0
Delsumma	2 310 000	2 310 000	2 310 000	2 310 000	2 310 000	11 550 000	0	11 550 000
Indirekta kostnader						0		0
Total projektkostnad	2 310 000	2 310 000	2 310 000	2 310 000	2 310 000	11 550 000	0	11 550 000

Motivering av sökt budget

Motivera kort varje sökt kostnad i den budget som du angivit.

Motivering av sökt budget*

Projektet rymmer, som framgår av forskningsprogrammet, en rad delprojekt, både djurexperimentella och kliniska. Den totala kostnaden, om alla de studier vi önskar genomföra skulle förverkligas, skulle bli väsentligen högre än det äskade beloppet. Vi hoppas att genom anslag från andra sponsorer kunna finansiera merparten av projektet, men inser att vi med all sannolikhet kommer att tvingas till priroiteringar som idag ej kan förutses, eftersom vi härvidlag kommer att låta oss vägledas av de resultat vi erhåller. Att ange "annan kostnad" i tabellen ovan blir härmed föga meningsfullt.

Annan finansiering

Ange forskningsresurser för projektet under perioden i form av övrig finansiering (sökt eller redan beviljad) utöver det som söks från Vetenskapsrådet. Ange hela beloppet, ej i tusental kronor.

Annan finansiering för detta projekt

Finansiär	Sökande/projektledare	Typ av bidrag	Dnr eller motsv.	2016	2017	2018	2019	2020	Totalt
1 ALF	Elias Eriksson			500	500				1 000
2 Hjärnfonden	Elias Eriksson	Sökt							0
3 FORTE	Elias Eriksson	Sökt							0
Totalt				500	500	0	0	0	1 000

CV och Publikationer

CV

Bifoga ditt och samtliga eventuella medverkande forskare CV i PDF-format, upprättat enligt instruktioner i utlysningstexten. Du kan endast bifoga en fil på maximalt 10 MB. Klicka först på mappsymbolen för att söka fram filen på din hårddisk, klicka sedan på plustecknet för att ladda upp filen i formuläret.

Förutom att du här bifogar ett fullständigt CV i PDF-format, ska du även under fliken CV hämta in uppgifter om din forskarutbildning från din profil i Prisma.

CV*

Se nästa sida för bilaga.

Curicculum vitae **Elias Eriksson March 2015**

Higher education qualification:

BM 1978; additional courses in MD program 1978-1980

Doctoral degree:

MedDr; 1988; pharmacology; Gothenburg; title: "Experimental psychoneuroendocrinology"; supervisor: Kjell Modigh,

Qualification required for appointments as a docent):

2000

Current position:

Professor of pharmacology, Gothenburg University, since 2001.

Previous positions:

Temporary assignments as junior physician (psychiatry), forskarassietent VR, forskare VR

Supervision:

Main supervisor for 19 PhD students, 13 of which have completed their PhD training:

Maria Carlsson 1995
Christer Nilsson 1998
Agneta Ekman 1996
Charlotta Sundblad 1996
Monika Hellstrand 2004
Hoi-Por Ho 2003
Jonas Melke 2003
Lars Westberg 2003
Marie Olsson 2002
Kristina Annerbrink 2009
Jessica Bah 2008
Olle Bergman 2009
Susanne Henningsson 2008

Ongoing:

Jakob Näslund (dissertation June 2015)

Erik Studer (dissertation June 2015)
Robert Pettersson (half time March 2015)
Fredrik Hieronymus
Fredrik Emilsson
Melker Hagsäter

Publikationer

Bifoga din och samtliga eventuella medverkande forskares publikationslistor i PDF-format, upprättat enligt instruktioner i utlysningstexten. Du kan endast bifoga en fil på maximalt 10 MB. Klicka först på mappsymbolen för att söka fram filen på hårddisk, klicka sedan på plustecknet för att ladda upp filen i formuläret.

Publikationer*

Se nästa sida för bilaga.

Peer-reviewed original articles

1. Lochner C, Hemmings S, Seedat S, Kinnear C, Schoeman R, Annerbrink K, Olsson M, Eriksson E, Moolman-Smook J, Allgulander C, Stein DJ: Genetics and personality traits in patients with social anxiety disorder: A case-control study in South Africa. Eur Neuropsychopharmacol, 17: 321-327 (2007).
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CV

Namn: Elias Eriksson	**Dr-examen:** 1985-05-17
Födelsedatum: 19560807	**Akademisk titel:** Professor
Kön: Man	**Arbetsgivare:** Göteborgs universitet

Forskarutbildning

Avhandlingens titel (sv)

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Namn: Elias Eriksson	**Dr-examen:** 1985-05-17
Födelsedatum: 19560807	**Akademisk titel:** Professor
Kön: Man	**Arbetsgivare:** Göteborgs universitet

Eriksson, Elias har inte lagt till några publikationer till ansökan.

Registrera

Villkor

Ansökan ska förutom av den sökande även signeras av behörig företrädare för medelsförvaltaren. Företrädaren är vanligtvis prefekten vid den institution där forskningen ska bedrivas, men ska i vissa fall utgöras av exempelvis rektor. Detta framgår i sådana fall av den aktuella utlysningstexten för bidraget.

Signering av *den sökande* innebär en bekräftelse av att:

- uppgifterna i ansökan är korrekta och följer Vetenskapsrådets instruktioner
- bisysslor och kommersiella bindningar har redovisats för medelsförvaltaren och att det där inte framkommit något som strider mot god forskningssed
- nödvändiga tillstånd och godkännanden finns vid projektstart, exempelvis avseende etikprövning.

Signering av *medelsförvaltaren* innebär en bekräftelse av att:

- den beskrivna forskningen, anställningen och utrustningen kan beredas plats inom institutionen under den tid och i den omfattning som anges i ansökan
- institutionen godkänner kostnadsberäkningen i ansökan
- projektet bedrivs i enlighet med svensk lagstiftning.

Ovanstående punkter ska ha diskuterats mellan parterna innan företrädaren för medelsförvaltaren godkänner och signerar ansökan.

Projektskisser ska ej signeras av medelsförvaltaren. Medelsförvaltaren ska endast signera den fullständiga ansökan om skissen går vidare till steg två.

Ansökningar där en organisation är sökande signeras automatiskt vid registrering av ansökan.