6

# Non-Response to Initial Antidepressant Therapy

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## 1. Introduction

Depressive and anxiety disorders are a major burden on society. Mood disorders affect 7% of the world's population, while severe forms of depression impact 2-5% of the US population (Murray and Lopez, 1996; Samuels and Hen, 2011). Furthermore, approximately 32-35 million adults in the US population (16%) experience an episode of major depression in their lifetime (Kessler et al., 2003). While many classes of drugs with antidepressant activity have been developed and approved (Wong et al., 2010), many patients do not respond to treatment (Trivedi et al., 2006). Therefore it is critical for basic research to develop animal models that present behavioral, neurochemical and brain morphological phenotypes reminiscent of depression and anxiety. Given that anxiety and depression have a high comorbidity with co-occurrence rates up to 60% in patients (Leonardo and Hen, 2006), animal models that present signs of both diseases could potentially be the most useful.

When prescribing medication, there is increasing pressure on clinicians to follow decision-tree medical algorithms, such as the Texas Medication Algorithm project (TMAP), in attempts to combat depression in patients that are non-responsive to initial lines of treatment. These involve multiple levels of treatments, each with varying success. Recently, STAR*D, a large study designed to mirror clinical practice, was conducted at 25 different sites. The study enrolled over 4000 patients with a broad range of symptoms and involved 4 possible steps for treatment (Fava and Covino, 2007). If patients failed to achieve remission at any level, they would be randomized for the next step of treatment. As patients moved from levels 2-4 of treatment, remission rates dropped dramatically (from approximately 35% at level 2 to 16% at level 4). Therefore, failure to achieve remission with 2 consecutive treatments is associated with very low remission rates in subsequent treatments. This suggests that the usefulness of current lines of treatment is limited and underscores the need for discovery of new treatments.

The present review defines the notion of non-response/resistance to antidepressants in human and the factors that may influence these clinical aspects. Then it focuses on the preclinical study aimed at developing relevant animal models of resistance including the unpredictable chronic mild stress (UCMS), the social interaction test and the repeated

corticosterone exposure. Is it worthwhile to model depression in rodents? Clearly many signs of depression such as guilt, feelings of worthlessness and recurrent thoughts of death are going to be features specific to humans. It is not possible to question animals and give them a score on the Hamilton Rating Scale for Depression (HAM-D) as is often done with humans. However, many other aspects of depressive disorders have been replicated in the laboratory setting. This review also describes the recent findings about the cellular and molecular bases of non-response and resistance to antidepressants. Finally, it synthesizes our current knowledge on the therapeutic activity of a new generation of antidepressant drugs, the triple reuptake inhibitors (TRIs). These pharmacological agents, that simultaneously increase serotonergic, noradrenergic and dopaminergic neurotransmissions, are believed to produce greater antidepressant effects than single- or dual acting-agents such as the selective serotonin reuptake inhibitors (SSRIs) or the serotonin/norepinephrine reuptake inhibitors (SNRIs) (Skolnick et al., 2003; Guiard et al., 2009). Indeed, by treating core and/or residual symptoms of depression, TRIs might provide an interesting alternative to the 50% of depressive individuals that do not respond adequately to conventional antidepressants.

## 2. Treatment-resistant depression (TRD) – Clinical aspects

SSRIs and SNRIs are the most commonly prescribed drugs for the treatment of major depression (MD). Despite recent advances in the pharmacological treatment of depression, 60% of patients with unipolar major depressive episodes do not respond adequately to SSRIs/SNRIs. Furthermore, as observed in the STAR*D study, treatment resistant depression, i.e. major depressive episodes resistant to antidepressant treatment, as defined by the lack of response to two consecutive and different antidepressant drugs, prescribed at adequate dosages and for adequate durations (Connolly and Thase 2011; Ruhé et al., 2011), occurs in 20% to 30% of MD patients (Gaynes et al., 2008). As compared with major depressive episode responsive to antidepressant drugs, treatment resistant episodes are associated with a 2 to 3-times increase in the use of other psychotropic medications. More importantly, the global medical costs associated with resistance are 6-times higher than those associated with non treatment-resistant depression ($42,344 vs. $6512) and the total depression-related costs of resistance are 19-times higher than those of patients with non-treatment-resistant MD ($28,001 vs. $1455) (Crown et al., 2002; Ivanova et al., 2010).

### 2.1 From non response to resistance: Definitions

Response to an antidepressant is usually characterized by a decrease of at least 50% from the baseline score in a depression scale at the end of the trial endpoint (Riso et al., 1997). Measurement of depression severity and antidepressant responsiveness is usually performed using scales such as the HAM-D, MADRS (Montgomery-Åsberg Depression Rating Scale), QUIDS (Quick Inventory of Depressive Symptomatology) and CGIs (Clinical Global Impression). However, such a decrease does not qualify a patient as remitted but only as responder, as patients with high scores (>30) at the HAM-D scale would not be consider as remitted (Nierenberg et al., 2001). Oppositely, the threshold for non-response is always hard to set and can exclude various sub-groups such as “non-remitted” responders as well as partial responders. Usually, non-response is considered to be a decrease of less than 25% on depression scale measurements, but in some studies, failure of remission can be

set as the threshold to define treatment failure. For instance, one of the largest studies aiming at defining effectiveness of SSRIs and identifying predictors of symptom remission was STAR*D, and its criteria were as following: an exit HAM-D score ≤7 qualified for remission and a reduction of more than 50% in baseline QIDS-SR (Quick Inventory of Depressive Symptomatology-Self Report) at the last assessment was defined as response (Hollon et al., 2005; Trivedi et al., 2006).

The definition of treatment resistance depressed (TRD) patients is still a matter of debate, and numerous definitions have been proposed based either on the duration of the illness, use of augmentation strategies or extent of treatment (Souery et al., 1999; Sackeim, 2001; Fagiolini and Kupfer, 2003), resulting in a possible under-estimation of TRD prevalence (Nemeroff et al., 2007). Furthermore, our knowledge of TRD is also based on naturalistic follow-up studies of the outcome of depressive disorders in general (Souery et al., 1999). The simplest and most widely used definition of resistance is when a current episode of depression has not benefited from at least 2 adequate trials (i.e. appropriate dose, duration and extent) of different classes of antidepressants (Ananth, 1998; Rush et al., 2003; Keller, 2005). Despite limitations (Berlim and Turecki, 2007a), this definition is the most widely accepted. Furthermore, this definition benefits from the strong support brought by the STAR*D study, where response rates after failure to 2 antidepressant strategies dramatically decrease (Ruhé et al., 2006b; Rush et al., 2006).

Staging methods for classifications of TRD have been proposed and reviewed by several authors (Berlim and Turecki, 2007b; Hetrick et al., 2008) and consist of graduating stages of resistance based on response to one or more different therapeutic strategies (Thase and Rush, 1997, see Table 1), but can also include chronic aspects of resistance (European Staging Model: Souery et al., 1999; Antidepressant Treatment History Form (ATHF): Sackeim et al., 1990; Oquendo et al., 2003). More recent models do not implicate an antidepressant hierarchy: for instance, the Massachusetts General Hospital staging method is a more flexible model, based on the number of antidepressant trials performed and their possible adjustments, without taking into consideration the pharmacological class differences of each trial (Fava, 2003). However this does not include duration of the disease. Yet one of the most comprehensive models proposed may be the Maudsley staging method for TRD (MSM). It incorporates the number of failed treatment trials, the chronicity of the disease and also includes measurements of disease severity as an important cofactor (Fekadu et al., 2009a,b). Ruhé et al. (2011) recently compared various staging methods and concluded that overall MSM displays high validity, but its reliability and sensitivity needs to be confirmed in other larger studies.

| Stage | Definition |
|---|---|
| **0** | Yet no adequate medication trials. |
| **I** | Non-response to 1 adequate trial of antidepressant |
| **II** | Stage I + non-response to 1 adequate trial of single antidepressant belonging to a distinct pharmacological class from that used in class I |
| **III** | Stage II + non-response to an adequate trial of a TCA |
| **IV** | Stage III + non-response to an adequate trial of a MAOI |
| **V** | Stage IV + non-response to electroconvulsive therapy |

Table 1. Staging method, adapted from Thase and Rush, 1997.

### 2.2 Factors implicated in non-response/resistance

Clinical, biological, and sociodemographic variables have been studied in relation to resistance to antidepressant treatment. However, due to sample size of the studies and methodological variablilities in defining resistance, results are not necessarily consistent and reliable (Berlim and Turecki, 2007a,b; Kornstein et Schneider, 2001).

#### 2.2.1 Sex differences in non-reponse/resistance

Women are twice as likely to experience MD as men (Kornstein et al., 2000) and four times as likely to have recurrent MD (Perugi et al., 1990). Women also have more MD symptoms and greater symptom severity (Angst and Dobler-Mikola, 1984; Frank et al., 1988; Young et al., 1990). Therefore, there is often a preponderance of women in studies, including treatment-resistant depression studies, but there is no evidence that sex is a predictor for resistance (Sotsky et al., 1991; Souery et al., 2007). The only sparse and slight evidence of sex differences might be in response to first antidepressant treatment (Sloan and Korstein, 2003), where women seem to respond slightly less to tricyclics (Hamilton et al., 1996), but respond similarly or slightly better to SSRI treatment (Papakostas et al., 2006; Kornstein et al., 2006). No sex difference to ECT treatment has been reported (Bloch et al., 2004).

#### 2.2.2 Age of onset

There is evidence that age of onset may predispose to a higher risk to develop TRD. Indeed, early onset of depression has been associated with a chronic course of the illness (Akiskal et al., 1981), and often results in higher severity of the disease as well as higher rates of comorbidity (Klein et al., 1999). Furthermore, early onset of first depressive episode has been considered as a risk factor in recent studies including large sample of patients (Dudek et al., 2010; Souery et al., 2007). Onset of depression in patients >60 years has been associated with a greater likelihood of psychotic symptoms and vascular brain changes that may increase the risk to develop to resistance (Kornstein et Schneider, 2001) Similar efficacy rates for antidepressant and psychological therapies have been reported in older adults and those under the age of 60 (Goldberg et al., 1998). TRD is clearly understudied in the elderly, because late-life depression has higher rates of physical and cognitive comorbidity and age-related pharmacodynamic/pharmacokinetic changes add greatly to the complexity of monitoring TRD (Cooper et al., 2011)

#### 2.2.3 Depression subtypes

Despite efforts to elucidate if TRD could be classified as "a unique subtype of depression" (Fagiolini and Kupfer, 2003), no specific endophenotypes or biological markers have been solely associated with TRD. Moreover depressive subtypes such as atypical depression, psychotic depression, and bipolar depression have been associated with poor outcome and a higher degree of resistance to specific types of treatment or to treatment in general, or both. Thus, depression subtypes are important elements as they may influence the rate of TRD, its evaluation and management. For example, patients with bipolar disorder may be misdiagnosed as TRD due to their higher rate of MD compared to manic episodes (Gaynes et al., 2009; Kupfer et al., 2002). Depressed subjects with melancholia have a greater degree of response to TCAs and ECT (Fava, 1996, 2003) whereas atypical depression is known to be

more resistant to TCAs but not to MAOIs (Liebowitz et al., 1988; Quitkin et al., 1993; Thase et al., 1991).

#### 2.2.4 Severity of the disease and other comorbid psychiatric disorders

Disease severity has been thoroughly associated with TRD (Souery et al., 2007; Dudek et al., 2010) and patients with greater symptom severity were approximately 3 times less likely to remit than those with mild or moderate depression in the STAR*D study (Rush et al., 2008). Severe depression is usually associated with lower spontaneous remission rate, greater risk of recurrence and higher chronicity of the disease (Thase et al., 2000). Disease chronicity has been also associated with TRD with longer episodes and greater recurrence of episodes (Souery et al., 2007; Dudek et al., 2010).

Comorbid anxiety is one of the most associated symptom coexisting with MD (Clayton et al., 1991) and thus is also one of the highest comorbidity of the disease associated with TRD (Gaynes et al., 1999; Souery et al., 2007; Dudek et al., 2010). Patients with melancholic features also appear more prone to develop TRD (Rush et al., 2008; Mc Grath et al., 2008). Obsessive-compulsive disorders, personality disorders, suicidal risk and substance of abuse (most of all is alcohol) are also among the greatest comorbidity associated with TRD (Souery et al., 2007; Kornstein et Schneider, 2001; Fagiolini et Kupfer, 2003; Sackeim, 2001). Finally, other medical conditions such as weight gain, diabetes, hypertension, hypothyroidism, chronic painful conditions are also considered as risk factors to develop TRD (Gaynes et al., 2009; Kornstein et Schneider, 2001; Berlim and Turecki, 2007a)

## 3. Animal models of depression and non-response/resistance to monoaminergic antidepressant

Given the problems with current lines of antidepressant treatment in the clinic, it is incumbent upon basic research to yield novel methods of treatment. In order for basic research to provide potential advances, a critical first step is to create useful animal models with relevant phenotypic features to reveal treatment responsiveness. However, some of the original animal models designed to address this problem suffered from a flawed tautological approach in that they were based solely on responsiveness to known antidepressants. Since no genetic variants with high penetrance that cause depression are known, animal models have mainly relied on different means of chronically exposing rodents to stressful experiences, or sensory tract lesions such as in olfactory bulbectomy, to induce behavioral states that present depression-like signs and are responsive to chronic antidepressant treatment.

### 3.1 Non-response/resistance in the unpredictable chronic mild stress model

The oldest most commonly used paradigm to induce a depression-like state is chronic mild stress (CMS). Initial observations suggested that animals subjected to multiple stressors over a prolonged period of time reduced their intake of saccharine or sucrose, a potential behavioral model of anhedonia (Katz, 1982). Furthermore, this effect was selectively reversed by chronic treatment with the TCA imipramine (Katz, 1982). Further work was able to repeat this result using more mild stressors, such as periods of food and water deprivation, small temperature reductions and changes of cage mates (Willner, 2005; Willner et al., 1987). Following these

studies the CMS procedure, and modified versions such as chronic unpredictable stress (CUS or UCMS), became commonly used and much work demonstrated that other depression-like changes were induced in animals, such as decreased sexual and aggressive behavior, decreased self-care, and altered sleep patterns (Willner, 2005). Furthermore these behaviors are all reversible by chronic, but not acute, treatment using multiple classes of antidepressants (Surget et al., 2008). While historically potential pitfalls of the CMS procedure are that it is notoriously labor intensive, and that there has been some difficulty in getting the procedure established and the results replicated across laboratories (Nestler et al., 2002), the modified versions of the CMS have proven more useful.

Recently, there have been some reports using CMS or variants to model treatment resistance in rodents. In one study, CMS significantly decreased sucrose consumption and the proliferation of adult hippocampal neural progenitors (Jayatissa et al., 2006). Following chronic treatment with a SSRI (escitalopram), the subjects were retested for sucrose consumption. A bimodal distribution was found where one group recovered (increased sucrose consumption) while another refracted treatment (no increase in sucrose consumption). Interestingly, there was a correlation between the animals in the group that recovered with a reversal of the decreased proliferation that was absent in the group resistant to treatment (Jayatissa et al., 2006). More recently, follow-up work has taken a proteomic approach in an attempt to find molecular differences in the ventral hippocampus between responders and non-responders (Bisgaard et al., 2007). Another study demonstrated that if animals are on a high fat diet during multiple UCMS procedures they become resistant to treatment with a SSRI (fluoxetine) (Isingrini et al., 2010).

### 3.2 Non-response/resistance in the social interaction model

A distinct procedure that has gained traction is the usage of a social defeat model. In this paradigm a mouse is forced into the territory of a mouse from a larger, more aggressive strain leading to an interaction resulting in intruder subordination. Repeated defeats over 10 days can result in a long lasting reduced social interaction, sexual dysfunction, sleep dysregulation, anxiety, metabolic deficits and anhedonia (Berton et al., 2006; Tsankova et al., 2006; Krishnan et al., 2007; Krishnan and Nestler, 2008). Interestingly, following the social defeat procedure there remains a large variance in behavior outcomes in spite of using an inbred mouse strain (C57BL/6). Some animals display a resistance to social defeat (resilience) while others are susceptible (determined by interaction with a social target relative to an empty enclosure). If animals are separated based on this measure, susceptible mice demonstrate decreased sucrose intake, a blunted circadian rhythm, and conditioned place preference to cocaine (Krishnan et al., 2007). Furthermore, phenotypes induced by social defeat in susceptible mice can be reversed by antidepressant treatment (Tsankova et al., 2006). Given that molecular mechanisms for resilience to the stressful procedure are now being worked out (Krishnan et al., 2007; Vialou et al., 2010), it would be intriguing to see if similar pathways are necessary for mediating response to antidepressants.

### 3.3 Non-response/resistance in the corticosterone model

A third procedure for inducing a depression-like state in animals is administration of chronic glucocorticoids in order to mimic the effects of chronic stress. A significant proportion of depressed patients display altered activity of the HPA axis, and stress

generally leads to hypersecretion of corticosteroids, which imposes an increased risk for depression (Carroll et al., 1981; Nemeroff et al., 1984; Strohle and Holsboer, 2003; Brown et al., 2004; de Kloet et al., 2005; Antonijevic, 2006; Leonardo and Hen, 2006, 2004). Chronic treatment of rodents with corticosterone effectively induces multiple anxiety- and depression-like changes in behavior, neurochemistry and brain morphology (Ardayfio and Kim, 2006; Gourley et al., 2008; Murray et al., 2008; David et al., 2009). Behaviorally, depression-related changes include suppression of sucrose intake and decreased self-care (Gourley et al., 2008; David et al., 2009), while anxiety-related changes include increased latency to emerge into the light compartment in the light/dark test, decreased time, entries and percent distance in the center of an open field and increased latency to take a bite of food in the novelty suppressed feeding (NSF) test (Ardayfio and Kim, 2006; David et al., 2009). Behaviorally, approximately 85% of C57BL/6 mice demonstrate anxiety and depression-related signs in response to chronic corticosterone, suggesting that, similar to social defeat, there is a small population that is resilient to the manipulation (David et al., 2009; David unpublished data). Interestingly, animal subjects that participate in the Novelty Suppressed Feeding test, a paradigm sensitive to chronic antidepressant, do tend to show a bimodal distribution in response to antidepressant treatment, suggesting a responder and non-responder divide (Samuels et al., 2011). By anthropomorphic analogy, an animal was considered as a responder to fluoxetine when its behavioral response was improved by at least 50%. Similarly to what is observed in humans, it was shown in this model that 30% of the animals did not respond to fluoxetine. These preliminary data argue for the validity of the CORT model in assessing non-response to antidepressants. Furthermore, we propose here a preclinical model for studying non-response/resistance, based on what has been developed in clinic by international consensus statement on major depressive disorder (Nutt et al., 2010) and proposed in therapeutic (Figure 1).

### 3.4 Current hypotheses on the molecular and cellular bases of non-response/resistance to antidepressants

It is still not clear why some animals are non-responders to antidepressants in these models. However growing evidence suggests that part of the answer lies in the neurogenesis process. At the cellular level, it has been known for several years that antidepressants increase hippocampal neurogenesis (Malberg et al., 2000) and that some of their behavioral effects require adult neurogenesis (Santarelli et al., 2003; Surget et al., 2008; Wang et al., 2008, David et al., 2009). However, in rodents deprived of adult neurogenesis, some behavioral effects of chronic antidepressant treatments remained unaltered suggesting the existence of neurogenesis-dependent and neurogenesis-independent mechanisms (Surget et al., 2008) (Figure 2). The delayed onset of antidepressants response in MD patients led to the hypothesis that their efficacy results from restoration of functional neural networks which are altered in MD patients (Duman et al., 2000). Thousands of new neurons are continuously produced every day in the mammal adult brain, specifically in the dentate gyrus (DG) of the hippocampus and the olfactory bulb (OB) (Lledo et al., 2006). In the DG, stem cells give rise to progenitor cells that migrate to the granular and molecular layers and differentiate into excitatory granule neurons. Neuroblasts fated for the adult OB are produced in the walls of the lateral ventricles (subventricular zone: SVZ). They migrate tangentially toward the core of the OB, forming the rostral migratory stream. Upon reaching the OB, adult born neuroblasts migrate radially within the lamina of the OB to reach their final position and

start to differentiate. In several animal models of depression, including the CORT model, chronic antidepressant treatments accelerate the three phases of hippocampal neurogenesis i.e. proliferation, maturation and survival of the newly born neurons (Wang et al., 2008). Interestingly, in some of the neurogenesis readouts (proliferation and maturation), the SSRI fluoxetine is much more effective in corticosterone-treated animals than in normal animals, suggesting that stress may increase the dynamic range in which fluoxetine can exert its effects on specific stages of neurogenesis. In humans, evidence suggests higher levels of neural progenitor cells in the DG of depressed individuals treated with SSRIs compared to untreated patients, who also had 50% fewer dividing cells than controls (Boldrini et al., 2009). Together these data are consistent with the hypothesis that part of antidepressant response is the stimulation of neurogenesis whereas non-response/resistance could potentially be explained by a lower capacity for neurogenesis.

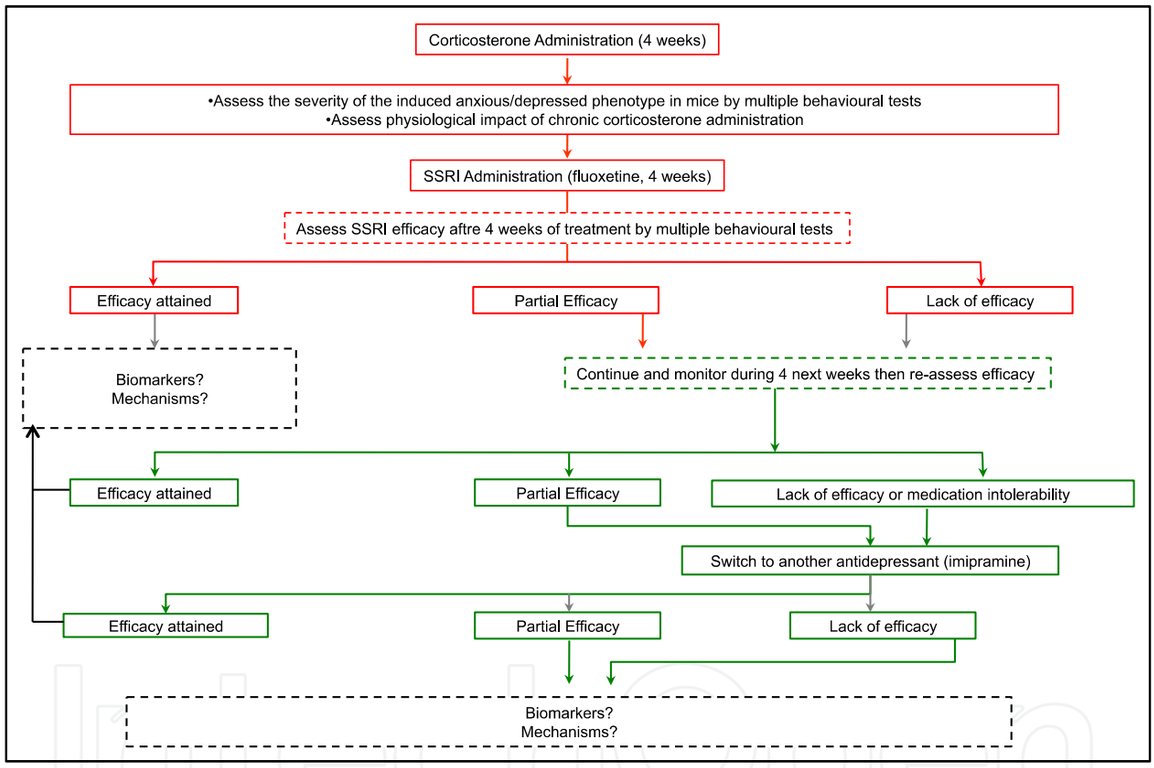


Fig. 1. Algorithm for developing animal model of resistance, based on the CORT model (David et al., 2009)

At the molecular level, Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, has been identified as a major candidate involved in the regulation of adult neurogenesis in the DG of the hippocampus and the OB (Duman and Monteggia, 2006; Bath et al., 2011). Indeed, chronic antidepressant treatments produce an increase in hippocampal BDNF levels (Nibuya et al., 1995; Duman & Monteggia, 2006) and a direct infusion of BDNF into the DG exerts antidepressant-like effects (Shirayama et al., 2002; Hoshaw et al., 2005; Kozisek et al., 2008). These observations raised the possibility that BDNF and activation of its high affinity receptor TrkB could be relevant markers of antidepressants response in MD patients, and blunted BDNF neurotransmission a marker of

non-response/resistance to these drugs. Among the main signaling pathways implicated in the pathophysiology of MD and antidepressant response, the β-arrestin-signaling cascade has recently gain attention due to the fact that BDNF may indirectly regulate this pathway. To date, four functional members of the arrestin gene family have been cloned, two arrestins (visual arrestin and cone arrestin) are expressed almost exclusively in the retina whereas two β-arrestins, β-arrestin 1 and 2, are ubiquitously expressed proteins with high levels in the brain (Luttrell and Lefkowitz, 2002). β-arrestins display two distinct roles. They constitute important proteins involved in the internalization of various receptors including 5-HT and DA receptors (Li and Jope, 2010). They are also scaffolds for G-protein-coupled receptors (GPCR) to recruit signaling molecules, one of the most fundamental cellular signal transduction processes known. Through this mechanism, β-arrestins activate intracellular kinases such as the protein kinase B (Akt) (involved in cell survival and proliferation), the extracellular-regulated kinase (Erk) (involved in cell proliferation, differentiation and survival) and the Glycogen Synthase Kinase-3β (GSK-3β) (involved in energy metabolism and neuronal cell development) (Lefkowitz and Shenoy, 2005). A substantial body of evidence has accumulated indicating that β-arrestins play a major role in the pathophysiology of mood disorders, as well as in the mechanisms of action of antidepressants. In human, for example, changes in β-arrestins expression are detected in MD patients and in response to stress while various antidepressant drugs reverse these changes (Avissar et al., 2004). Overall, these data suggest that β-arrestins could be major molecular determinants of the effects of fluoxetine, and, more generally, of SSRIs and SNRIs. β-arrestin-1 protein and mRNA levels in mononuclear leukocytes of untreated patients with MD are significantly lower than those of healthy subjects and these levels are significantly correlated with the severity of depressive symptomatology (Avissar et al., 2004; Schreiber et al., 2009). The low β-arrestin-1 protein and mRNA levels were alleviated by antidepressant treatments, whereby normalization of β-arrestin-1 preceded, and thus predicted, clinical improvement. In rodent, SSRIs, SNRIs but also non-selective reuptake inhibitors increase β-arrestin-1 levels. Molecular functions of β-arrestins place them in pathways associated with response to lithium, a drug currently used to treat bipolar disorders (Beaulieu et al., 2008). Caron's group had hinted that β-arrestin KO mice were unable to scaffold a signaling complex. Hence, in these mutants, lithium failed to activate Akt, leading to a loss GSK3 inhibition and to a disruption of antidepressant-like responses. Several sources of evidence suggest that SSRIs promote inhibitory control of GSK3 in several brain regions including the frontal cortex, the hippocampus and the striatum of naïve mice exhibiting a normal, non-depressed phenotype (Emamian et al., 2004; Li et al., 2007; Beaulieu et al., 2008) suggesting that inhibition of this protein play a major role in the antidepressant response. Consistent with this hypothesis, GSK3 inhibitors produce antidepressant-like effects in the mouse FST (Gould et al., 2004). Similar results were observed in GSK3 mutant mice, which display a 50% reduction in the expression of this kinase (Hoeflich et al., 2000). With respect to β-arrestin-2, recent findings show that this protein might be also involved in neurogenesis-dependent and –independent mechanisms (David et al., 2009; Li et al., 2009). Using the "CORT model", it was shown that fluoxetine reversed the neurogenic deficit induced by glucocorticoid elevation and restored expression of β-arrestin-1 and -2 that were blunted by chronic corticosterone (David et al., 2009). These observations further confirm the possibility that β-arrestins are necessary for antidepressant to exert their therapeutic activity. Accordingly, deficient mice for β-arrestin-2 displayed a reduced response to fluoxetine (David et al., 2009). Together, these data led us to postulate that decrease in the expression

and/or functional activity of molecular components of β-arrestin-signaling cascades represent biomarkers of non-response and resistance to antidepressant.

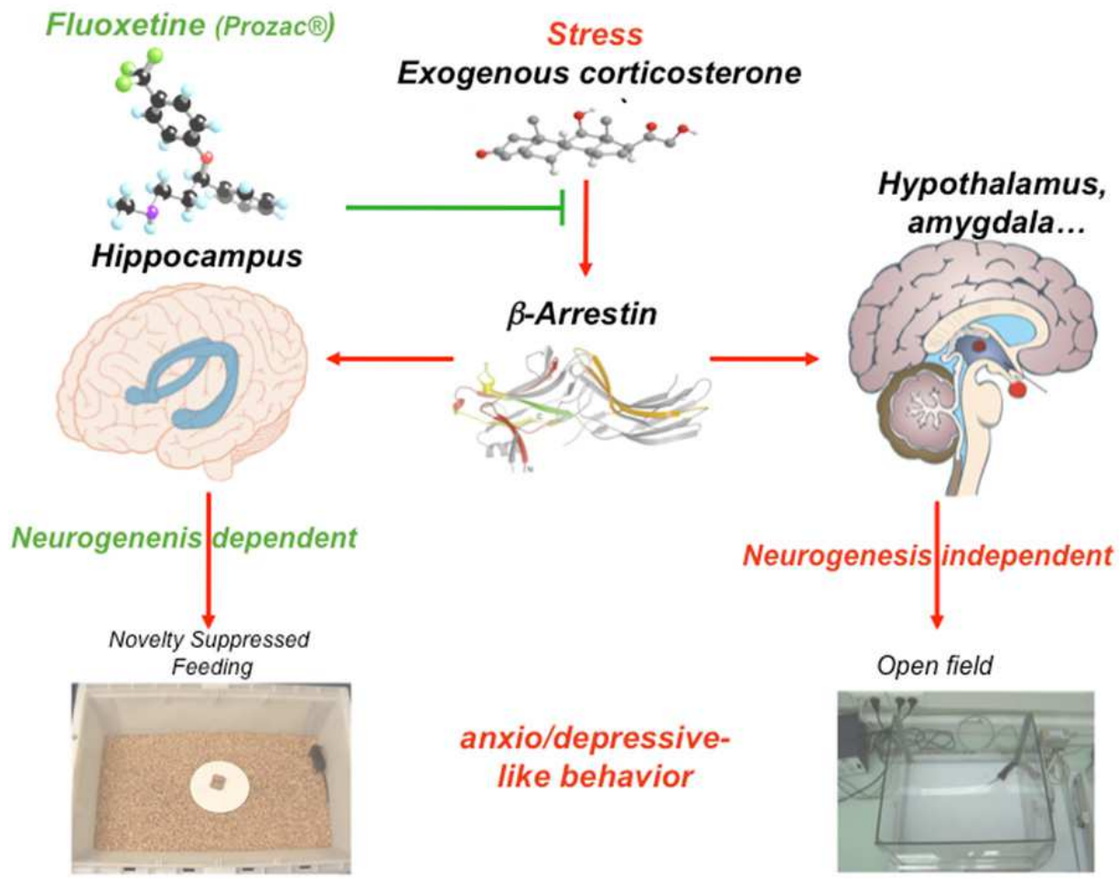


Fig. 2. Chronic fluoxetine reverses the behavioral and neurogenic deficits induced by chronic corticosterone exposure, showing neurogenesis-dependent and neurogenesis-independent effects (Adapted from Rainer et al., 2009).

## 4. New antidepressant strategy to counteract resistance: The triple reuptake inhibitors (TRIs)

Numerous therapeutic strategies have been proposed to alleviate TRD, including augmentation strategies such as the combination of SSRIs with bupropion or antipsychotics, combination of drugs with ECT or somatic treatments such as repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS), or new molecules including the triple reuptake inhibitors (TRIs).

Signs and symptoms of depression can be linked to one or more monoaminergic systems, specifically the 5-HT, the NE and the DA systems. There are considerable reciprocal interactions between these monoaminergic neurons that can produce counterproductive effects (Guiard et al., 2008). When using a SSRI, for example, 5-HT transmission is enhanced, but at the same time there is a dampening of the activity of NE and DA neurons through inhibitory 5-HT2A and 5-HT2C receptors, respectively. This could explain the residual

symptoms of fatigue, lack of energy, and anhedonia, often observed after patients present an overall positive response to a SSRI (Blier and Briley, 2011). Using dual-acting agents such as duloxetine, milnacipran or venlafaxine would result in an additional increase in NE activity. However, a risk inherent in increased NE activity is that of provoking anxiety. Hence, the question can be asked as to whether the remaining symptoms observed with SSRI/SNRIs are responsible for a non-response/resistance to these antidepressants or if the lack of significant therapeutic activity results from dysfunction in other neurotransmitters such as a blunted DA neurotransmission? In this context, a new generation of antidepressants named the triple reuptake inhibitors (TRIs) has been developed with the hope of offering a clinically relevant advantage over currently available medications (Guiard et al., 2009). Since TRIs simultaneously enhance extracellular levels of 5-HT, NE and DA neurotransmissions in various brain regions, this class of antidepressants could exert their therapeutic activity by treating more symptoms of MD and/or by attenuating some side effects observed in response to traditional antidepressants. Accordingly, converging lines of evidence indicate that drugs enhancing dopaminergic neurotransmission can diminish anhedonia (Dunlop and Nemeroff, 2007), a symptom that responds poorly to SSRIs (Shelton and Tomarken, 2001). Clinical studies indicate that it is possible to achieve an antidepressant action by enhancing DA. Moreover, the dopamine reuptake inhibitor bupropion has also demonstrated antidepressant activities (Tremblay and Blier, 2006) and its use in combination with SSRIs enhances the antidepressant response in resistant patients (Zisook et al., 2006).

### 4.1 Preclinical properties of TRIs

A number of compounds with the ability to bind and block all three monoamine transporters have been developed with the hope to produce greater symptomatic relief than single- or dual-acting agents and consequently to reduce non-response and resistance. DOV Pharmaceutical, Inc. is the first company having provided in vitro and in vivo preclinical data with their triple reuptake inhibitors DOV216303, DOV21947 (amitifadine) and DOV220075 (bicifadine). New molecules have followed such as NS2330 (tesofensine, GlaxoSmith-Kline/NeuroSearch), SEP225289 (Sepracor Inc.), CNS-1 and CNS-2 (Albany Molecular Research Institute Inc), PRC-025, PRC-050, PRC-200SS (Mayo Foundation), JNJ7925476 (Johnson & Johnson Pharmaceutical Research & Development), WF-23 (Eli Lilly), JZAD-IV-22 (PsychoGenics) and more recently TP1 (Luye Pharmaceutical Group). Others compounds will undoubtedly emerge in a near future. In 2010-2011, the structure activity relationship (SAR), of at least eleven new TRIs, has been reported (Hache et al., 2011).

#### 4.1.1 Behavioral effects of TRIs

Behavioral data clearly demonstrated the antidepressant-like effect of TRIs that act by increasing the time of mobility and/or by reducing the time of immobility in the FST or the TST. Among the TRIs tested, JNJ7925476 appears the most potent since a low dose of this agent (0.3 mg/kg; s.c.) produced antidepressant-like effects. In term of efficacy (i.e., maximal effect), compounds such as PRC200-SS (10mg/kg; ip), D-142 or D-161 produced a greater percentage of increase in the time of mobility or decrease in the time of immobility than the others TRIs (Aluisio et al., 2008; Dutta et al., 2008; Liang et al., 2008; Dutta et al., 2011). Interestingly, JNJ7925476 and PRC200-SS display the highest affinity for SERT and NET

suggesting that this double action is an important prerequisite to produce optimal behavioral responses. Since DA is known to enhance locomotor activity, the possibility cannot be excluded that TRIs increased the time of immobility in these various studies, through a psychostimulant effect. In various studies, however, TRIs did not modify locomotor activity at doses that produce antidepressant-like effects (Tian et al., 2011; Aluisio et al., 2008; Liang et al., 2008; Shaw et al., 2007; Skolnick et al., 2003), thereby ruling out the possibility that the antidepressant-like activity detected does not appear to be from "false-positive" results. An important drawback in the development of antidepressants is the fact that the new compounds are tested after acute administration in naïve, non-depressed animals. Their chronic use in animal models is more appropriate and provides more informative results to determine whether or not new pharmacological agents are worth being tested in clinical trials. A recent study in bulbectomized rats provided some interesting results. In this model, a 14-day regimen of the TRI DOV216303 normalized bulbectomy-induced hyperactivity in the open field, similar to the effect of imipramine at the same dose (Breuer et al., 2008). Inevitably, further studies in these animal models are required to determine the potential of TRIs over SSRIs and SNRIs in terms of quality of antidepressant response.

### 4.1.2 Neurogenic effects of TRIs

As above-mentioned (paragraph 3.4), a number of studies have demonstrated that SSRIs increase cell proliferation and neurogenesis in the DG of the hippocampus of naive (Marcussen et al., 2008; Sairanen et al., 2005; Santarelli et al., 2003; Malberg et al., 2000) or depressed rodents (David et al., 2009; Malberg and Duman, 2003). It was also reported that catecholamines (NE and DA) might stimulate this process. For example, NRIs and SNRIs have been shown to increase the local expression of neurotrophic factors including BDNF (Nibuya et al., 1995; Larsen et al., 2008; Russo-Neustadt et al., 2004) and adult hippocampus neurogenesis in the DG (Malberg et al., 2000). In a recent study aimed at comparing monoaminergic compounds with different pharmacological profiles (at doses that have been shown to produce antidepressant-like effects in behavioral models), it was demonstrated that sustained administration of the reuptake inhibitors venlafaxine and imipramine increased BDNF mRNA expression after 7 and 14 days of administration respectively, while the SSRI fluoxetine had no effect (Larsen et al., 2007). It is thus possible that the activation of the serotonergic and noradrenergic neurotransmitter system activates different downstream cascades that are both able to increase the transcription of BDNF. Whether or not this apparent effect favors antidepressant response has yet to be demonstrated. Importantly, the hippocampus receives a sparse dopaminergic innervation from the ventral tegmental area (Scatton et al., 1980), raising the possibility that DA and related receptors play a limited role in the local regulation of BDNF expression and neurogenesis. However, dopaminergic denervation in animals causes a dramatic reduction in the number of proliferating cells in the hippocampus (Hoglinger et al., 2004) while the stimulation of DA receptors with selective D2 agonists has recently been shown to enhance neurogenesis in the DG of the hippocampus (Hoglinger et al., 2004, Yang et al., 2008). In a recent series of in vivo experiments, it has been shown that the Cytokine Ciliary Neurotrophic Factor (CNTF), abundant in astrocytes close to dopaminergic terminals, constitutes an endogenous regulatory component of D2-receptor-dependent neurogenesis in DG (Yang et al., 2008; Mori et al., 2008) suggesting that TRIs might be stronger on neurotrophic factor gene expression, neural plasticity, and neurogenesis than SSRIs, NRIs and SNRIs. Using in situ

hybridization, an initial study showed that treatment with the TRI NS2330 (Tesofensine), for 5 and 14 days had no effect on BDNF expression in the granular cell layer, while increasing its expression by 35 % in the CA3 after 14 days (Larsen et al., 2007). Furthermore, NS2330 stimulated the number of neuroD-positive cells after 14 days treatment and the nuclear marker of proliferation Ki67, confirming the antidepressant potential of this novel agent (Larsen et al., 2007). Although these results revealed a strong effect of NS2330, the net effect of blockade of each of the monoamine reuptake sites remains unknown. Further studies are truly necessary to dissect the contribution of each monoamine uptake target on the regulation of BDNF or others neurotrophic factors gene expression. It is possible that the stimulation of the expression of various neurotrophic factors such as BDNF and CNTF induced by the concomitant enhancement of central 5-HT, NE and DA transmission, might contribute to shorten the delay of action of traditional antidepressants drugs.

### 4.2 Clinical properties of TRIs

TRIs are in process of development (Millan, 2009) and most are now in Phase II clinical trials. A small citalopram-controlled trial of DOV216303 in severely depressed patients yielded significant improvements in Hamilton Depression Rating Scale (HAM-D) scores in both groups at one-week and two week time points (Skolnick et al., 2006). DOV Pharmaceutical has recently reported the results of a multi-centric, randomized, double-blind, placebo-controlled study with amitifadine (DOV21947) in 61 patients with MD (Tran et al., 2011). For the primary outcome measure, treatment with amitifadine was associated with a significantly greater improvement in the MADRS and CGI-I total score at week 6 compared with placebo. In addition, a significantly greater remission rate for the CGI-S was observed with amitifadine compared with placebo at week 6. This study also showed that amitifadine was efficacious in improving anhedonia, a core symptom of depression that is presumed to be related to a hypodopaminergia. Despite these encouraging data, it is still not clear whether non-response and/or resistance to TRIs is lower than that observed with SSRIs or SNRIs. Specific clinical trials should address this question in the future. Nevertheless, several arguments allow for optimism. 75% of patients suffering from depression are found to report somatic symptoms, including various types of pain such as headaches, stomach pain, back pain, and vague, poorly localized pain (Fava, 2003). A recent study has shown that responders who have not achieved remission have significantly more somatic symptoms than remitters following 8 weeks of treatment with fluoxetine. These data may suggest that antidepressants that are particularly effective in the treatment of pain and painful physical symptoms may yield higher remission rates in major depressive disorder (Hache et al., 2011). In addition, it has been suggested that presence of pain may be an indicator of MD that may have poorer treatment outcome with an initial SSRI (Leuchter et al., 2010). Acute and chronic pains may result from reduced levels of endogenous 5-HT, NE and DA activities, at both the spinal and supraspinal levels (Ren and Dubner, 2002). Thus, one would expect a better efficacy of dual-or triple-acting agents over selective 5-HT or NE reuptake inhibitors in analgesia (Hache et al., 2011). Several open-label randomized controlled clinical trials, meta-analyses, and systematic reviews have confirmed the clinical efficacy of selected antidepressants in persistent pain conditions (Dharmshaktu et al., 2011). Clinical studies have corroborated that bicifadine is an effective analgesic in the treatment of postoperative pain (Krieter et al., 2008). In a second study, the TRI NS7051, has shown comparable antinociceptive properties to tramadol confirming the interest of these antidepressants in the relief of pain (Munro et al., 2008). The molecule has undergone several

phase II and III trials for the treatment of pain, including acute postsurgical pain and chronic low back pain, and is being evaluated for painful diabetic neuropathy (clinical trial.gov).

## 5. Conclusion

In summary, current antidepressant treatments are not sufficient, as many patients do not respond. Future basic and clinical research will need to take new approaches to advance the understanding and discover new methods for treatment-resistant depression. While most animal models of depression have focused on pharmacological validity, this has led to an overemphasis on mechanisms underlying currently used drugs rather than the discovery of new targets that could benefit patients suffering from treatment-resistant depression. Furthermore, using animal models will be valuable in providing a translational framework to study SSRI insensitivity, and validation of any findings in humans as potential biomarkers for treatment responsiveness will pave the way to break a tradition of using SSRI sensitive behavioral assays to interrogate novel approaches for relieving depressive phenotypes.

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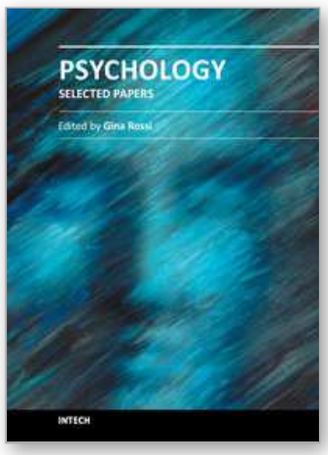


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This book represents a selection of chapters that address several topics from the broad domains of psychology: alcoholism, clinical interventions, treatment of depression, personality psychology, qualitative research methods in psychology, and social psychology. As such we have interesting blend of studies from experts from a diverse array of psychology fields. The selected chapters will take the reader on an exciting journey in the domains of psychology. We are sure the content will appeal to a great audience.

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