Lithium's Antisuicidal Efficacy: Elucidation of Neurobiological Targets Using Endophenotype Strategies

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Key Words

aggression, impulsivity, mood stabilizer, suicidal behavior, personality traits, pharmacotherapy

Abstract

Lithium used as a drug treatment for major mental disorders such as bipolar disorder and depression is effective in reducing the risk of both attempted and completed suicide. However, the mechanisms underlying lithium's antisuicidal actions are not yet known, limiting the development of novel lithium-mimetic compounds that may help reduce suicide risk with fewer undesirable side effects. Suicide is a complex behavior, complicated to study in humans, and impossible to fully reproduce in animal models. The endophenotype approach, by which quantitative measures of neurobiological function are used to assess and subclassify psychiatric illness, may present a path to new discoveries. Aggression and impulsivity are candidate endophenotypes strongly associated with suicide; we review the evidence supporting aggression and impulsivity as suicide endophenotypes, as well as the effects of lithium on these constructs in both humans and rodents. Examining the mechanisms that contribute to lithium's antiaggressive and antiimpulsive effects may assist in understanding how lithium acts to reduce the risk of suicide and in elucidating the neurobiological underpinnings of suicidal behavior.

INTRODUCTION

Suicide is a public health concern throughout the world. Recent statistics from the U.S. Centers for Disease Control indicate that suicide was the eleventh leading cause of death in 2005 for all age groups, accounting for over 32,000 deaths, or 1.3% of all deaths in the United States (1). Suicide rates vary by gender, with males typically completing suicide four times more often than females, and females attempting suicide two to three times more often (1). Psychiatric illnesses, including schizophrenia and especially a history of affective illness, are among the strongest predictors of suicide (2–5). Despite a robust increase in the pharmacological treatment of psychiatric disease (particularly depression with antidepressants), the rates of suicidal thoughts, suicide attempts, and completed suicides have not decreased over recent years (6).

In 1949, John Cade published the first report suggesting a mood stabilizing property of the element lithium (7). This discovery came after he noticed a sedating effect of lithium following administration to guinea pigs. Noting this calming effect, Cade investigated lithium's effects on mania in ten human subjects and found lithium to be effective in treating acute manic episodes. The results from a number of double-blind studies have subsequently confirmed the efficacy of lithium both in the acute treatment of mania and for mania prophylaxis (8). In addition, lithium shows efficacy in treating depression and appears most effective as an adjunct treatment for depression (see 9, 10 for meta-analysis and review). As reviewed below, extensive evidence has also accumulated that indicates lithium is effective in the prevention of attempted and completed suicide. Clozapine, an atypical antipsychotic used in the treatment of schizophrenia and related disorders, is the only other medication reproducibly shown to decrease the risk of suicidal behaviors (11, 12). Multiple studies employing various designs have consistently shown that there is a lower rate of suicidal behavior associated with lithium therapy (13) (**Figure 1**). Other drugs used in the treatment of bipolar disorder and major depression (such as anticonvulsants and antidepressants) lack substantial evidence of an antisuicidal action (14–16). Despite its clinical effectiveness, the mechanisms by which lithium exerts antimanic, antidepressant, or antisuicidal effects are unknown.

Although lithium is an effective medication for reducing the risk of suicide, it also has numerous side effects. Lithium has a narrow therapeutic window, with optimum serum levels in the range of 0.5–1.2 mM, which requires that individuals on lithium be closely monitored. Thyroid impairment, polydipsia, polyuria, weight gain, tremors, and diabetes insipidus are among the side effects; these and other side effects often lead to problems with patient adherence and discontinuation (4, c.f. chapter 21). Without knowledge about the therapeutic targets of lithium, it is impossible to use hypothesis-driven approaches to develop lithium-mimetic compounds that effectively reproduce the efficacy of lithium without its side effect profile. It is therefore imperative to elucidate the neurobiological mechanisms underlying lithium's efficacy in order to develop more effective and better-tolerated medications to be used in the treatment of mania and depression, and—the focus of this review—the prevention of suicide.

LITHIUM AND SUICIDE RISK REDUCTION

One of the first reports to suggest an antisuicidal effect of lithium was published in 1974 (17). Prien et al. reported the results of two randomized, placebo-controlled studies; one was conducted with bipolar subjects and the second with a combination of bipolar and unipolar patients. Combined data from the studies indicated that among the placebo group two suicides were observed, yet none were seen in the lithium treatment group, suggesting that lithium might have a protective effect against suicide. A number of studies examining the effect of lithium have compared suicidal behavior in subjects before and during lithium treatment. Lepkifker et al. (18) focused on unipolar subjects who had been maintained on lithium therapy for at least one year; results showed that subjects had fewer

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

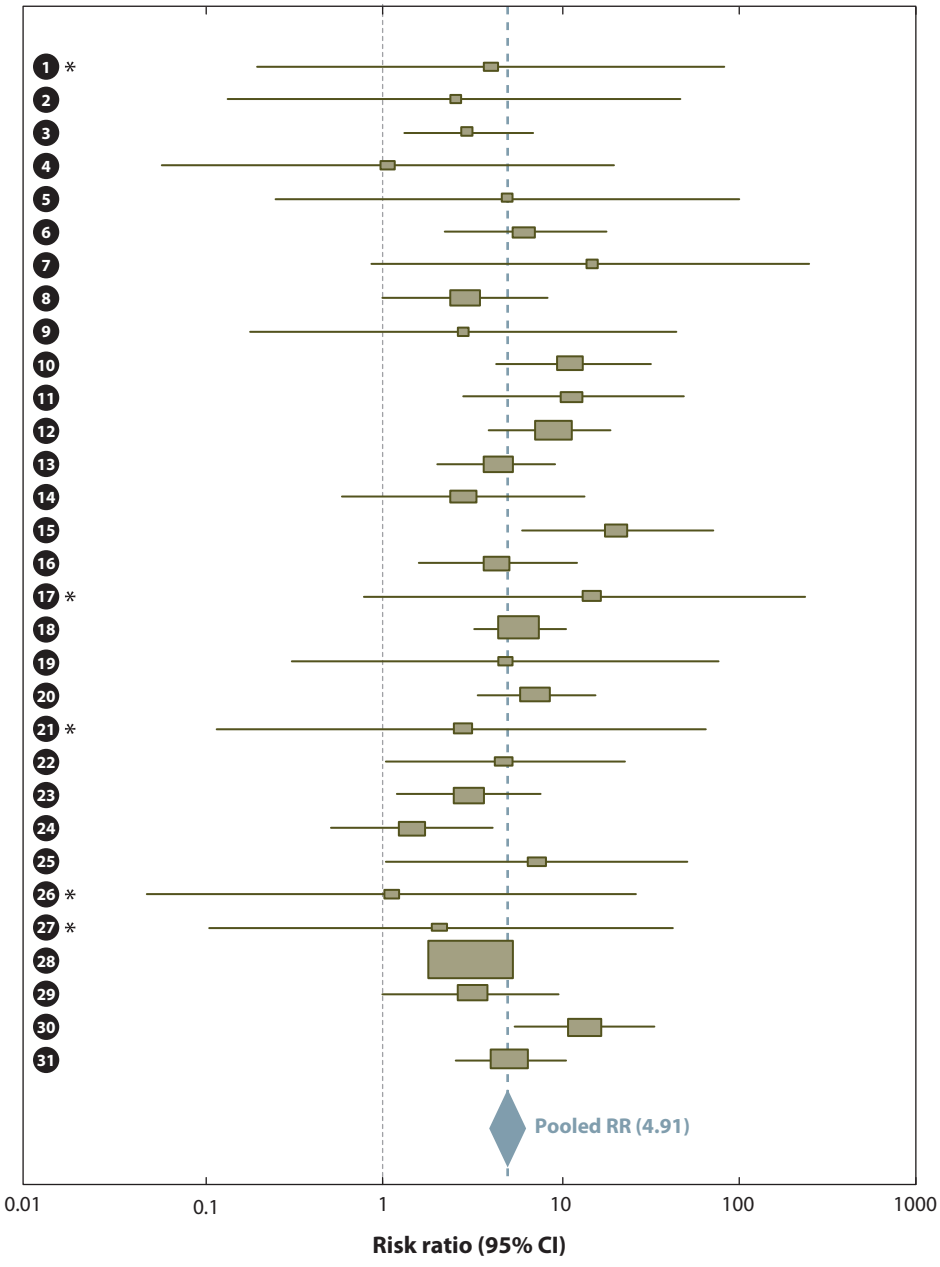


Figure 1

Risk of suicides and/or attempts with lithium treatment in mood disorder patients. This figure displays forest plot risk ratios (RRs) as brown squares proportional to study weight and their 95% confidence intervals (CIs) in 31 studies that had two arms (with and without lithium treatment) (see 13 for a complete description of the methods). The pooled RR of not on lithium versus on lithium (*blue diamond*) = 4.91 (95% CI 3.82–6.31, $z = 12.5$, $p < 0.0001$). For a list of references (*numbers in black circles*) used in **Figure 1**, see **Supplemental Appendix A** by following the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org.** *Indicates randomized, controlled trials. (Reproduced and modified with permission from Reference 13.)

suicide attempts and suicidal thoughts when on lithium compared with the period before starting lithium. Later,Tondo et al. (19) reported that suicidal acts decreased in a cohort of bipolar subjects maintained on lithium therapy for at least one year when suicidal acts in this period were compared both with the period before lithium and, in some cases, to the period after lithium discontinuation. Nilsson (20) assessed suicide rates in patients with mood or schizoaffective disorders treated with lithium for at least one year. When comparing completed suicide rates between patients when off versus when on lithium treatment, he found a 4.8 times higher risk of suicide.

Prospective studies have also assessed the antisuicidal effects of lithium. Assessing subjects with a prior suicide attempt (and thus a high subsequent risk of suicide) and at least one year of continuous lithium treatment, Bocchetta et al. found that continued lithium treatment was associated with a 6-fold reduction in suicide attempts and a 24-fold reduction in completed suicides (21). A discontinuation study by Müller-Oerlinghausen et al. following manic patients found that suicidal behavior was evident in 85% of subjects who discontinued lithium treatment and in only 11% of subjects who remained on lithium for the study duration (22). Theis-Fletchner et al. conducted a randomized, prospective, multi-center study of patients with affective illness (23), during which 378 subjects were randomized for at least two years to lithium, carbamazepine, or amitriptyline. No suicidal acts were observed in the lithium group, but substantial risk was seen in the other groups; five attempted and four completed suicides in the carbamazepine group, and five completed suicides in a group that contained patients who had discontinued their randomized medication during the study period. Angst et al. followed 406 subjects admitted for mania, depression, or both between 1959 and 1963 until 2003 (24); patients treated with lithium had lower standardized mortality ratios (SMR) for death by suicide (5.7) compared with untreated patients (16.5). Additionally, the SMR for overall mortality in lithium-treated patients (1.2) was significantly lower than in untreated patients (1.7) and was not significantly different from the general population. Another report described bipolar subjects, who were followed for ten years, and again found a lower incidence of suicidal behavior with lithium treatment (25). Subjects with low treatment adherence showed a 5.2-fold increased risk of suicidal behavior than individuals who adhered to lithium treatment.

Large retrospective cohort studies provide additional evidence for an antisuicidal efficacy of lithium. Examining HMO data, Goodwin et al. found that the risk of suicide was 2.7 times higher during treatment with valproic acid (Depakote®) than during treatment with lithium (14). Additionally, nonfatal suicidal behaviors resulting in hospitalization and attempts diagnosed in the emergency room were reduced with lithium therapy compared with treatment with valproic acid. Another group, using data from Oregon's Medicaid program, reported a similar outcome (16). The lowest rates of attempted and completed suicide among those receiving various mood stabilizers were seen in the lithium treatment group (16).

The studies reviewed above do not include every study examining the antisuicidal effect of lithium, and are mentioned to provide an overview of the breadth and depth of the existing studies. Numerous meta-analyses have been completed, and include additional studies. Tondo et al. performed a meta-analysis that included 28 studies involving more than 17,000 patients with major affective illness (26). The results from these 28 studies indicate that lithium led to an 8.6-fold lower risk of suicide compared with the risk without lithium. In the three studies that did not show an antisuicidal effect of lithium, it was determined that the length of lithium treatment was short and probably inadequate. Looking at seven randomized controlled trials, Cipriani et al. found lithium to be more effective in reducing the risk of suicide, deliberate self-harm, and overall mortality than placebo, anticonvulsants, or antidepressants in subjects with mood disorders, as fewer suicides and deliberate self-harm events were seen in the lithium groups across the studies (15). Baldessarini et al. analyzed open and controlled trials together and found that the incidence of

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

suicidal behavior across 45 studies was sixfold lower with lithium treatment. When the 31 studies with non-zero suicide risks in at least one treatment arm were included, the incidence of suicidal acts was still five times lower with lithium treatment (13) (**Figure 1**). When assessing attempted and completed suicide seperately, similar results were found. Another finding of this meta-analysis was that lithium treatment appeared to reduce the lethality of suicide attempts, as evidenced by fewer fatalities per attempt. A recent meta-analysis reviewed eight studies of lithium-treated patients with recurrent major depressive disorder and found that the risk of suicidal behavior in major depressive disorder patients was 88.5% lower with lithium treatment (27).

The results of these studies suggest that lithium is effective in reducing suicidal thoughts, attempts, and completed suicide in both bipolar and unipolar patients. It is possible that lithium exerts these effects by reducing affective symptoms, but there is evidence that this effect of lithium is specific and does not result from improvement of the underlying mood disorder. Müller-Oerlinghausen et al. examined high-risk affective disorder patients with a history of at least one suicide attempt before beginning lithium prophylaxis (28, 29). They divided these subjects into three groups: poor responders who showed less than a 50% improvement in terms of affective episodes, excellent responders who showed no further episodes, and moderate responders, which included the rest of the subjects. Although the clinical response to lithium was different among these three groups, a statistically significant reduction in suicide attempts was seen in all three as compared with the rates of attempts before lithium treatment was started. These data suggest that lithium may be exerting an antisuicidal effect that is separate from its effect on affective episodes. Although lithium has clear adjunct antidepressant effects, it is generally considered inferior to some other antidepressants when used as monotherapy (30–32). This finding, as well as the fact that other, often faster acting and at least equally effective, antidepressants and mood stabilizers do not appear to have similar antisuicidal efficacy, suggests that the antisuicidal efficacy of lithium is not due solely to its ability to stabilize mood.

As we describe in the following sections, there is a strong biological and genetic basis for suicide risk. Trait impulsivity and aggression are associated with an increased risk of suicide. Furthermore, lithium has been shown in numerous animal and human studies to reduce impulsivity and aggression; thus, modification of these traits may mediate the mechanism of lithium's antisuicidal effect (13–15, 27–29, 33).

EVIDENCE SUPPORTING A BIOLOGICAL BASIS TO SUICIDE

The results of a large number of studies implicate a biological predisposition toward suicide (34). Suicidal behavior appears to be familial, independent of psychiatric diagnoses (35, 36). For example, Brent et al. showed that first-degree relatives of suicide completers had higher rates of both suicide attempts and completions, and this relationship remained after adjusting for an Axis I diagnosis (35). Adoption studies also provide evidence of a genetic basis to suicide. The biological relatives of adopted individuals who died by suicide have been shown to have higher rates of suicide than the suicide completers' adopted relatives, and the biological parents of adoptees who committed suicide had higher rates of suicide than the biological parents of control adoptees (37). It has also been observed that monozygotic (MZ) twins have a higher concordance rate for suicide than dizygotic (DZ) twins, which is suggestive of a genetic component to suicide (36, 38). Egeland & Sussex examined rates of suicide in an Amish community, which is thought to lack many risk factors for suicide because the communities typically do not engage in alcohol or drug use, have little or no unemployment, and stress close ties both within and between families (39). This study determined that three quarters of all suicides originated in only four family pedigrees (which equates to roughly 16% of that Amish community). Additionally, although affective disorders also

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

loaded heavily in these families, the reverse was not seen: there were families with heavy loading for affective disorders but no suicides.

Studies examining the serotonin (5-HT) system in suicide attempters and completers demonstrate abnormalities that also suggest a biological basis for suicidal behavior (34). Cerebrospinal fluid (CSF) 5-Hydroxyindoleacetic acid (5-HIAA, the major metabolite of serotonin) has been shown in multiple studies to be lower in suicide attempters and completers than in controls (40–42). In the prefrontal cortex of suicide completers, the amount of serotonin transporter binding sites has been reported to be lower than in controls (43, 44). Further alteration of the serotonin system is evidenced by higher levels of 5-HT_{1A} and 5-HT_{2A} receptor binding in postmortem brain tissue from suicide completers as compared with noncompleters (43, 45).

Several genes have been found to be associated with suicidal behavior (46, 47). Candidate genes for suicidal behavior include the genes for tryptophan hydroxylase (TPH1 and TPH2), the serotonin transporter (5-HTT), catechol-O-methyltransferase (COMT), and nitric oxide synthase types I and III (NOS I and NOS III) (46–48, 48a, 48b). As depicted in **Figure 2**, some of these genes are also linked to endophenotypes associated with suicide.

Additional evidence for a neurobiological component in suicide derives from the fact, reviewed above, that lithium therapy is associated with a decrease in the incidence of suicide. In addition to the potential to develop lithium-mimetic medications with an improved side effect profile, understanding the molecular mechanism by which lithium acts to decrease suicidal behavior would undoubtedly lead to a better understanding of the neurobiology of suicide. Conducting pharmacological studies on suicide has inherent problems, including ethical concerns as well as issues with obtaining adequate sample sizes. Suicide is a relatively rare event, with current data estimating that 11.01 suicides occur per 100,000 people per year (1). In general, it is difficult to conduct prospective studies with suicide as an outcome variable because a very large sample is necessary.

It can be advantageous to look at candidate endophenotypes of suicide to study the neurobiological basis of suicide as well as to develop animals models or tests that reflect the underlying neurobiology of suicide (49). An endophenotype is a measurable component that lies along the pathway between the disease of interest (in this case suicide) and the genotype (50). Generally considered to be trait markers, they are stable over time unless acted on by an outside intervention such as a medication. The pharmacology related to the underlying neurobiology of suicide could be dissected with fewer risks to patients by testing the effects of pharmacological agents on suicide endophenotypes in animals. Endophenotypes are hypothetically simpler to study than the full disease manifestations, and they can be neurophysiological, endocrinological, biochemical, neuroanatomical, cognitive, or neuropsychological in nature. The approach has proven to be valuable in other areas of medicine, including the study of complex diseases such as diabetes and coronary artery disease. Simple measures such as the glucose tolerance test, serum cholesterol levels, and sphygmomanometer measurements of blood pressure have proven invaluable in diagnosing, classifying, and modeling these diseases in animals. Endophenotypes associated with schizophrenia, such as impairments in working memory and prepulse inhibition, are proving remarkably useful in dissecting the neurobiology of this complex psychiatric disease (50). Importantly, using the unaffected relatives of cases to measure the same endophenotypes enhances the statistical power of such studies. The remaining portion of this review focuses on potential suicide endophenotypes and the evidence that lithium modifies particular endophenotypes in humans or animals.

CANDIDATE SUICIDE ENDOPHENOTYPES

A number of candidate suicide endophenotypes have been suggested (**Figure 2**). These include biological measures such as CSF 5-HIAA levels, altered hypothalamic-pituitary-adrenal (HPA)

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

axis activity, and low levels of cholesterol (51). Neuroimaging findings such as the brain response to fenfluramine-induced serotonin release are additional possibilities (52). Other potential endophenotypes include a number of heritable personality traits, some of which are supported by extensive research (52a). Personality can be readily quantified using self-report data from suicide attempters and their relatives, or by psychological autopsy methods. These strategies allow for the quantifiable measurement of a personality trait and subsequent comparison between individuals exhibiting suicidal behavior and controls. Several traits such as neuroticism, harm avoidance, and hopelessness have been found to be associated with suicide attempts or completion using these methods (53–56). However, the most reproduced association between suicide and personality appears to be with measured indicators of aggression and impulsivity. These constructs are related, and many studies have examined impulsive aggression in populations with suicidal behaviors. It is difficult to determine whether this construct is a separate endophenotype, or rather is a subtype of aggression (or a subtype of impulsivity). This review, in most cases, focuses on aggression and impulsivity as separate constructs; for this reason, studies that measured impulsive aggression are interpreted as potentially measuring both constructs.

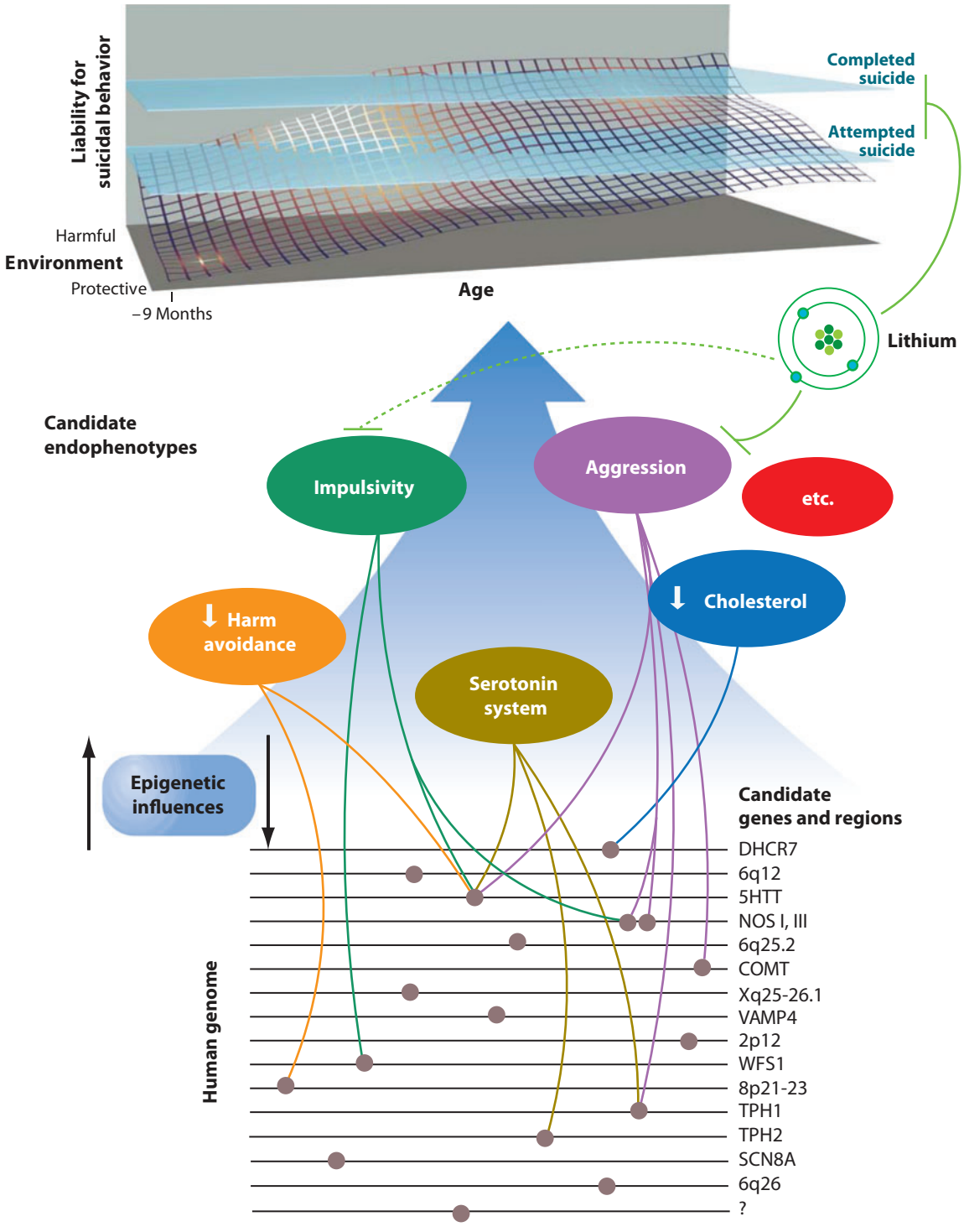
Heritability is a generally accepted endophenotype criterion, and studies have confirmed the heritability of aggression and impulsivity (50) (**Table 1**). Twin studies have shown that MZ twins have higher correlations on measures of aggression than DZ twins (57–60). These studies estimate that between 47 and 54% of variance in measured aggression is heritable. Another twin study examined MZ and DZ twins reared together or apart and found that, in both circumstances, the MZ twins showed a greater correlation of aggression scores than the DZ twins, further emphasizing the genetic contribution to aggression (61). Similarly, impulsivity has been shown to have a heritable component. Two studies compared MZ and DZ twins that were reared apart or reared together (62, 63). In both of these studies, which each used a different measure of impulsivity, the MZ twins showed higher concordance on the measures, regardless of whether they were reared together or apart, than the DZ twins. As discussed below, the results of numerous studies of suicide attempters, completers, and their biological family members have shown increased levels of aggression and impulsivity (and also impulsive aggression).

Evidence for Aggression As a Suicide Endophenotype

Aggression has long been linked to suicide. Freud theorized that suicide was aggression turned inward (64). In 1938, Menninger suggested that suicide had its roots in aggression and, in 1939, Dollard proposed the frustration-aggression hypothesis of suicide (65, 66). This theory states that suicide results from aggression (elicited by frustration) that an individual is unable to express owing to fear of punishment, and thus the individual displaces this aggression onto himself. Following these early theories, researchers began conducting studies to determine if people with suicidal behavior did indeed show higher levels of aggression. The results of numerous retrospective, prospective, and family studies lend support to the notion that suicide is associated with higher levels of aggression.

An early retrospective study that specifically examined measures of aggression in suicide attempters compared these individuals with nonsuicidal psychiatric inpatients as well as to normal controls (67). The suicide attempters had experienced significantly more violent events, defined as traffic accidents, accidents requiring medical attention, interpersonal fights, and drug and alcohol problems. While these variables are not ideal measures of aggression, the results of this study gave early evidence of a link between suicidal behavior and aggression. Assessing young female suicide attempters, Cantor reported a link between aggression and suicide. Aggression was measured using a questionnaire, and the suicide attempters showed elevated aggression scores

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.



Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

Table 1 Criteria for endophenotypes and studies supporting impulsivity and aggression as candidate endophenotypes associated with suicidal behavior

Endophenotype Criteria	Studies on Aggression	Studies on Impulsivity
An endophenotype is associated with illness in the population	(69–74)	(70, 71, 73, 79–81)
An endophenotype is heritable	(57–61)	(62, 63)
An endophenotype is state independent (but may be modified by drugs)	(73, 74)	(73, 74*, 81)
Within families, endophenotype and illness cosegregate	(35, 74, 77*)	(74*, 77)
An endophenotype identified in probands is found in their unaffected relatives at a higher rate than in the general population	(78)	No studies identified

The above studies demonstrate that aggression and impulsivity satisfy specific endophenotype criteria (for explanation of criteria see References 49, 50). The studies are representative of those described in the review, and are not exhaustive. For example, almost all studies demonstrate that aggression and impulsivity are state independent, as actively suicidal subjects are seldom studied. * Indicates that the evidence is based on impulsive aggression for that particular study within that column.

when compared with nonattempters (68). Mann et al. focused on psychiatric patients, and used standard self-report measures of aggression [the Buss Durkee Hostility Inventory (BDHI) and the Brown Goodwin Aggression Inventory]. Suicide attempters again showed higher levels of aggression compared with nonattempters (69). When a logistic regression model was performed, the authors found that the variable of aggression/impulsivity characterized individuals as suicide attempters regardless of their psychiatric diagnosis. In 2001, Brodsky et al. assessed psychiatric patients with major depressive disorder and found that individuals with at least one suicide attempt scored significantly higher on the Brown Goodwin Aggression Inventory, indicating a higher level of aggression among those with suicidal behavior (70). Another study examined individuals with bipolar disorder and again, those with a previous suicide attempt showed higher levels of aggression on the same scale than those without an attempt (71). This association also seems to hold for suicide completers. Brent et al. compared adolescent suicide completers with demographically similar adolescent controls using the psychological autopsy method; the suicide completers had higher levels of lifetime aggression than the controls (72).

Prospective studies have also found an association between higher levels of aggression and suicidal behavior. In a study by Oquendo et al., psychiatric patients were followed for two years after researchers assessed several personality traits, including aggression (73). In the follow-up period, suicide attempts were recorded; individuals who later attempted suicide had initially shown higher levels of aggression as measured by self-report. Additionally, the factor of aggression/impulsivity

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Figure 2

Candidate gene regions, genes, and endophenotypes implicated in a biological systems approach to suicide research. The top portion depicts the dynamic interplay among genetic, environmental, and epigenetic factors that produce cumulative liability to demonstrating thoughts and behaviors related to suicide. Lithium therapy is associated with a decreased risk of suicide attempts and completed suicide (13), which may be due in part to moderating effects of the drug on aggression and impulsivity. The clinical and preclinical evidence for an antiaggressive effect of lithium is strong, while an antiimpulsive effect is not as clear, as is indicated by solid versus dashed lines connecting lithium and these endophenotypes. None of the sections of this figure can be definitive; many more gene loci, genes, candidate endophenotypes, and links among the three remain to be discovered. Similarly, there are many gene loci, genes, and candidate endophenotypes that were not included owing to space limitations and the conceptual limitations of this figure. (Please see the following references for a more extensive discussion: 34, 36, 46–48, 51, 53. In addition, the reader is referred to the web site **http://gmes.mcgill.ca/** by the McGill Group for Suicide Studies, which contains a comprehensive database of genetic association studies related to suicidal behavior.)

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

was a significant predictor of future suicidal acts. Another prospective study found that familial transmission of suicidal behavior appeared to be mediated by transmission of impulsive aggression (74). The study examined offspring of probands with mood disorders, more than half of whom had a previous suicide attempt (none of the offspring exhibited prior suicidal behavior). Baseline aggressive traits were measured with self-reports, and the offspring were followed for six years. At the end of the study, the offspring who had attempted suicide were compared with those who did not attempt suicide, and the attempters showed higher levels of aggression at baseline. The parents of these attempters were more likely than parents of nonattempters to have attempted suicide themselves, and they also showed higher levels of aggression than parents of nonattempters.

Family studies provide additional support for the association of aggression and suicide. Pfeffer et al. examined prepubertal children and followed them for six to eight years (75). The sample consisted of psychiatric inpatients with a history of suicide attempts, inpatients with suicidal ideation, nonsuicidal inpatients, and healthy controls. First-degree relatives of the subjects with attempts or ideation reported a significantly higher history of assaultive behavior. Johnson et al. compared adolescent suicide attempters and their first-degree relatives with nonsuicidal psychiatric controls and their first-degree relatives (76). Suicide attempters with high BDHI assault subscale scores had higher rates of suicide in their first-degree relatives. Brent et al. compared adolescent suicide completers and their families with controls and their families (35). The psychological autopsy method was used to gain information about the suicide and control probands, and self-report tests were given to family members so that their psychological and personality traits could be assessed. Among the suicide probands, families with a higher loading for suicide attempts also showed higher ratings of aggression. This led the authors to conclude that the transmission of aggression between generations may be involved in the transmission of suicidal behavior. Brent et al. also examined impulsive aggression and suicidal behavior in mood disordered probands and in their siblings and offspring, finding that suicidal behavior in the probands was associated with higher impulsive aggression (measured by the BDHI) in both the probands and their offspring (77). They determined that the most powerful predictor of suicide in the offspring was the transmission of impulsive aggression. A similar study examined male suicide completers and compared them with age- and gender-matched controls (78). Aggression was defined as a lifetime history of repeated instances of verbal or physical aggression toward others, and was a dichotomous variable. There was a significantly higher level of aggression in the first-degree relatives of suicide completers compared to the first-degree relatives of the controls. The results of these family studies suggest that the candidate endophenotype of measured aggression is also present at higher levels in family members of individuals that exhibit suicidal behavior.

Evidence for Impulsivity As a Suicide Endophenotype

Impulsivity is another personality trait that has been strongly associated with suicidal behavior. Impulsivity can be inferred from an individual's behavior patterns (gambling, poor decision making, etc.), or measured by self-report questionnaires and in the laboratory. Retrospective studies have focused on suicide attempters and their levels of impulsivity. In the same study mentioned with aggression, Cantor used a questionnaire to compare the level of impulsivity exhibited by suicide attempters and nonattempters; the results indicated that suicide attempters had higher levels of impulsivity (68). Using the Baratt Impulsivity Scale, another study examined patients with major depressive disorder and found that the self-reported levels of impulsivity were higher among suicide attempters than among nonattempters in this psychiatric population (70). The authors reported that the level of trait impulsivity (and also aggression) and not the objective severity of depression was significantly associated with suicidal behavior. Grunebaum et al., using scores on

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

the Baratt Impulsivity Scale, reported that bipolar suicide attempters scored higher on the measure of impulsivity than did nonattempters (71).

Another retrospective study assessed suicide attempters using a behavioral laboratory measure of impulsivity, the immediate memory task from the continuous performance test (CPT) (79). This test requires subjects to remember a five digit number and indicate when that number is flashed onto a computer screen. Commission errors, which occur when a subject responds to a number that is similar to the original but not identical, are thought to indicate impulsivity. In this particular study, all the subjects had bipolar disorder. Individuals who had a previous history of suicide attempts had significantly more commission errors (responded impulsively) on the immediate memory task. A similar laboratory test of impulsivity was used in a study by Dougherty et al. in 2004: They used the immediate memory task and also included another version of the CPT, the delayed memory task (80). Similar to the previous study, more commission errors were seen in individuals with a past history of suicide attempts than in nonattempters. Additionally, when separated based on the number of attempts, subjects who had two or more attempts showed higher levels of impulsivity than those with one attempt who, in turn, scored higher than those with no attempts.

In addition to retrospective studies examining impulsivity and suicidal behavior, several prospective studies have been carried out that compared baseline traits in relation to future suicidal behavior. A study by Caspi et al. (81) examined behavioral characteristics of a cohort of toddlers and followed these children into adulthood. At age 21, the group that had initially been labeled as impulsive showed a higher frequency of suicidal behavior than the normal group of toddlers. This suggests that impulsivity at a young age predisposes to suicidal behavior later in life. A separate study followed mood disorder patients for two years; the subjects who attempted suicide during the follow-up had higher scores on a self-report of impulsivity at the beginning of the study (73). The study by Melhem et al. in 2007 followed the offspring of patients with mood disorders and examined their impulsivity and suicidal behavior. The offspring who attempted suicide during the six-year follow-up period had higher levels of impulsivity (and impulsive aggression) at baseline than offspring who did not attempt suicide (74).

Family studies are another method used to investigate the link between suicide and impulsivity. Brent et al. followed probands with mood disorders who had or had not attempted suicide and their offspring (77). Among suicidal probands, those who had siblings who also attempted suicide showed the highest levels of impulsivity (as well as impulsive aggression). This suggests that suicide and impulsivity may load together in families, and further strengthens the impulsivity-suicide relationship.

The results of these many studies provide strong evidence that both aggression and impulsivity are associated with suicidal behavior, and are candidate suicide endophenotypes (Table 1). Studies of individuals before or after a suicide attempt typically show that these individuals have higher rates of aggression and impulsivity compared with nonattempters from both control and psychiatric populations.

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

THE EFFECTS OF LITHIUM ON CANDIDATE ENDOPHENOTYPES OF SUICIDE, IN HUMANS

Lithium and Aggression in Humans

The results of a number of studies suggest that lithium has antiaggressive properties in humans (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org** to **Supplemental Table 1*a***). The earliest published reports on the antiaggressive effects of lithium were case reports describing a few subjects. One of the first such described

a woman with homicidal tendencies and self-destructive behaviors who stabilized with lithium treatment (82). Another case report focused on a patient with a six-year history of impulsive and violent behavior (83). This patient was treated with lithium and, for the follow-up period of 18 months, experienced no further violent episodes. Wickham & Reed published a review of lithium's effects on aggression, and included a case series involving ten subjects (84). The subjects ranged in age from 16 to 64, all had a long-standing history of aggressive behavior, and all improved with lithium therapy. Although these case reports did not have rigorous controls, placebo comparison groups, or strict criteria for defining aggression, they nonetheless offered early insight into the possible efficacy of lithium in the treatment of aggression.

Open- and single-blind studies have since been conducted. Prison populations contain highly aggressive individuals, and thus an enriched population in which to investigate lithium's antiaggressive properties. An early study by Sheard in 1971 involved 12 prisoners who showed a propensity for aggression both before and during their incarceration (85). The study was performed in a single-blind, within subject, placebo cross-over manner. Using self-report measures of feelings of anger and a daily record of the number of verbal and nonverbal aggressive acts, a significant decrease in aggression was found with lithium treatment. A nonblinded study conducted in a prison population included prisoners who showed recurrent patterns of aggression (86). Data gathered from psychiatric staff, guards, and administrators showed that there were statistically fewer violent infractions during compared with before lithium treatment. Furthermore, the prisoners reported a decrease in aggressive feelings while taking lithium. Another open study focused on children and adolescents diagnosed with conduct disorder and displaying aggression (87). The study used the Overt Aggression Scale (filled out by the nursing staff) as well as the Global Clinical Consensus Rating (GCCR). During the fourth and final week of treatment, the scores on the Overt Aggression Scale were significantly lower then before treatment, whereas the number of aggressive acts was significantly higher the first week compared with the last week of lithium treatment, with all eight patients showing an improvement on the GCCR.

Several double-blind, placebo-controlled studies have been conducted. One study involved a crossover design with eight female patients in a psychiatric hospital (88). Lithium and placebo were given alternately for four weeks, and nursing staff rated aggressive behavior on a seven-point scale. The group showed a significantly lower aggression score during periods of lithium treatment. Another study by Sheard involved 66 prisoners and used as an outcome measure the number of infractions of prison rules (89). For the first and fifth months, the prisoners received no treatment, and lithium treatment was given during the second, third, and fourth months. The number of major infractions, defined by threatening behavior and assaults, as well as total number of infractions was significantly reduced during the lithium treatment period. In 1987, Craft et al. studied 42 mentally handicapped patients (90). There was a four-week placebo run-in period, followed by 12 weeks of treatment with lithium or placebo. Aggression was assessed daily by the nursing staff using a five-point scale. Aggression scores for the lithium-treated group were significantly lower throughout the treatment period than the scores for the placebo group.

A study by Campbell et al. focused on 61 children hospitalized for conduct disorder with aggressive features (91). There was a two-week placebo period in which baseline behaviors were assessed; this was followed by random assignment to lithium, haloperidol, or placebo for four weeks. Scores from the Children's Psychiatric Rating Scale showed that both haloperidol and lithium significantly reduced aggression and hostility compared with placebo. The same group looked at children with this diagnosis in a later study comparing lithium with placebo (92). A two-week placebo period was utilized, followed by a six-week period of random treatment with either lithium or placebo and another two-week placebo period. A statistically significant decrease was seen in the Children's Psychiatric Rating Scale aggression factor during the treatment phase

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

among those who received lithium compared with those who received placebo. In 2000, Malone et al. conducted a study involving subjects aged 10 to 17 with a diagnosis of conduct disorder (93). A two-week placebo period was used for baseline assessment, and only those subjects who continued to show at least three acts of aggression per week were randomized to lithium or placebo for four weeks. The outcome measures of the Global Clinical Judgments Scale, the Clinical Global Impressions, and the Overt Aggression Scale showed a reduction in aggression scores with lithium treatment compared with placebo. Rifkin et al. also examined the effects of lithium in adolescents with conduct disorder (94). This study utilized a one-week placebo period, and only those subjects who continued to show aggression were randomized to lithium or placebo for two weeks. There was no statistical difference between the placebo and lithium groups when comparing scores on the Overt Aggression Scale (1 out of 12 in the placebo group improved, 3 of 14 in the lithium group improved). However, this negative result may be viewed with caution because lithium was administered for only two weeks and lithium may require a longer treatment period to exhibit its antiaggressive effects in this particular population.

The results of a majority of these studies suggest a strong antiaggressive effect of lithium across various populations with differing diagnoses and ages (**Supplemental Table 1*a***). This effect is seen with various outcome measures, including self reports, behavioral indexes of aggression, and ratings by medical personnel.

Lithium and Impulsivity in Humans

The results of several studies suggest that lithium decreases impulsivity, although overall, the evidence for such an attenuating effect is not as strong as for aggression (**Supplemental Table 1*b***). Fewer studies have looked at impulsivity as a main outcome of lithium treatment, but the ones that have suggest lithium decreases impulsive behaviors. Thus, the limited amount of data concerning the effects of lithium on impulsivity appears due to a lack of research rather than a lack of positive results per se.

A few double-blind placebo-controlled studies have been conducted to assess lithium's effect on impulsivity. Dorrego et al. compared lithium and methylphendidate in adults with attention deficit-hyperactivity disorder (ADHD) (95). The study consisted of 32 subjects who underwent a two-week washout period of all psychotropic medicines, followed by eight weeks of lithium or methylphenidate, two weeks of washout, and eight weeks of the other drug. Methylphenidate and lithium both led to significantly lower scores on the impulsivity subscale of the Conner's Adult ADHD rating scale. Hollander et al. conducted a study of 29 pathological gamblers with bipolar spectrum disorders (96). The subjects were off psychotropic medications for at least two weeks prior to the study and were randomized to lithium or placebo for ten weeks. In the lithium-treated group, the severity of gambling was lower than in the placebo group at the end of the study, suggesting a decrease in impulsivity associated with lithium treatment. The subjects who took and responded to lithium showed a significant decrease in the nonplanning subscale of the Barratt Impulsivity Scale, whereas those who responded to placebo showed no improvement on any of the subscales of the Barratt Impulsivity Scale (response was defined as being much or very much improved on the Clinical Global Impression gambling subscale). A treatment study involving 179 bipolar disorder subjects randomized to placebo, valproic acid, or lithium for three weeks also assessed impulsivity as a secondary measure. A measure of impulsivity was aquired by nurse ratings based on their observations of the subjects' impulsive behaviors, and both the lithium and valproic acid groups showed significant improvement compared with controls (97). Several other factors were examined, including anxious pessimism, hyperactivity, and hostility, but impulsivity was the factor that most distinguished treatment with lithium and divalproex from placebo.

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

The results of these studies suggest that lithium decreases impulsivity (**Supplemental Table 1*b***). However, additional well-controlled studies examining the effects of lithium on impulsivity are needed to improve the strength of this conclusion.

THE EFFECTS OF LITHIUM ON CANDIDATE ENDOPHENOTYPES OF SUICIDE, IN RODENTS

Lithium and Aggression in Rodents

There is extensive evidence that lithium reduces aggression in rodents (98; **Supplemental Table 2*a***). Rodent tests of aggression often pair two members of the same species in a test of social conflict. Aggressive behaviors are recorded by a trained observer when two rodents encounter one another, and measures may include bite attacks, tail rattles, lateral threat, and chasing. A common and simple method used to elicit aggression in rodents is through isolation of the animals. Rodents that have been housed individually for a period of one to four weeks tend to show higher levels of aggression than animals that have been group housed. An isolated animal can then be paired with an unfamiliar, group-housed animal in the resident-intruder test. In this test, a group-housed animal (intruder) is placed in the cage of an isolated animal of the same species (the resident), and subsequent attack behaviors by the resident toward the intruder are scored. A variation of this test places both animals in an unfamiliar arena or cage. Another test of aggression, commonly called shock-induced aggression, uses minor electrical shock to provoke the rodents into assuming fighting behaviors.

The above paradigms generally use male mice or rats, which are naturally more aggressive than females. When studying female rodents, the maternal aggression paradigm is employed, in which a nursing female housed with her pups is confronted with a male intruder. Typically, the female will attack this unfamiliar male and aggressive acts such as bites and tail rattles may be observed.

Shock-induced aggression has been a focus of research to test lithium's effects on aggression in animals. The studies reviewed below all involved rats. Sheard gave lithium injections to rats and found that lithium significantly increased the latency to attack (99). Additionally, the lithium-treated animals did not fight at the two lowest shock intensities, while the saline-treated animals did show aggression at these intensities. Eichelman et al. subjected rats to the shock-induced paradigm and found that injections of lithium chloride led to a statistically significant decrease in fighting (100). A separate study by Mukherjee & Pradhan in 1976 confirmed these results; the frequency of attacks decreased in the shock-induced paradigm in lithium-treated animals compared with saline-treated animals (101). Marini et al. found that, when rats were treated with lithium, they exhibited a lower percentage of fighting than control rats (102). Prasad and Sheard examined shock-induced aggression and found that lithium treatment led to a significant decrease in aggression (103). In this study, they also administered desipramine (an antidepressant drug) to the rats and found that it increased aggression. When lithium was given along with the antidepressant, lithium was shown to be effective in blocking the increase in aggression. Our lab has recently shown that lithium administration also decreases shock-induced aggression in mice without affecting social interaction or dominance (C.E. Kovacsics & T.D. Gould, unpublished data). However, these data, as well as data from rats, may be confounded by effects of lithium on shock sensitivity (104; C.E. Kovacsics & T.D. Gould, unpublished data).

An early study by Sheard used Sprague Dawley rats and subjected them to the resident intruder test (105). Intruder rats were given P-chlorophenylalanine (PCPA; an inhibitor of tryptophan hydroxylase that results in depletion of brain 5-HT), amphetamine, or brain lesions, and the residents received lithium in their drinking water. The author reported that, with lithium, the resident rats showed no significant aggressive behavior (105). Later, Malick used mice in the same

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

paradigm and found that a single injection of lithium did not affect aggression, but five days of lithium treatment inhibited aggression in a dose-related manner (106). Another study in 1985 found that, when mice were given lithium (or carbamazepine), isolation-induced aggression in the resident-intruder paradigm was reduced (107). The most recent investigation of lithium in the resident-intruder paradigm compared lithium- and valproate-treated mice with controls (108). Both drugs were shown to decrease aggression without affecting social interaction.

Other less common methods of asessing aggression have also been studied in relation to lithium's antiaggressive efficacy. One study used clonidine or nialamine plus L-Dopa to induce aggression, and placed groups of four mice together for an observation period of one hour (109). Aggression was defined as the number of biting attacks, and the results of the study show lithium administration potentiated the increased aggression in both groups. Another study modified the resident-intruder paradigm (110). In this study, both mice were isolated, treated with injections of lithium chloride, and fighting occurred in a clean cage that neither mouse had previously been exposed to. Higher doses of lithium (4.5 and 6.0 meq kg^{-1} day^{-1}) led to a decrease in aggression compared with controls. Another study examined the effects of lithium on rank-related fighting and maternal aggression in mice (111). The animals were housed in groups of six, and received daily lithium injections. The rank-related fighting test paired a male mouse in his home cage with an unfamiliar mouse that was anosmic (by administration of a 4% zinc sulfate solution in the nose, these mice lost their sense of smell) and thus showed little to no aggression. In this test, lithium treatment decreased aggression. Maternal aggression was tested by adding a male mouse to the cage of a nursing female and her pups, and lithium did not show an effect on this type of aggression (111). The majority of these results show that lithium has an antiaggressive effect, but they also suggest there may be a limit to this effect depending upon the test utilized.

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

Lithium and Impulsivity in Rodents

Few studies have examined the effects of lithium on impulsivity in rodents (**Supplemental Table 2*b***). To our knowledge, the only studies that purport to assess lithium's effects on impulsivity in animals have focused on the measure of attack latency. A suggested measure of impulsive aggression is of the latency to first attack in the resident-intruder or similar paradigm (with a shorter attack latency indicating higher levels of impulsivity) (112). This is a simple measure. However, one inherent problem is that it is not clear whether it is a measure of impulsivity, aggression, or perhaps a mixture of both constructs; for the purposes of this review, we include this measure in the discussion of both aggression and impulsivity.

In the 1970 study by Sheard reviewed above, he reported that lithium treatment of rats resulted in an increase in the attack latency in the shock-induced aggression test compared with vehicle-treated rats (99). In the rank-related test performed by Brain & Al-Maliki, lithium was again shown to increase the latency to attack in this measure of aggression (111). There is a clear lack of data on lithium's effects on impulsivity in animals, as the above studies are the only two that could be located to include in this review. This likely reflects a lack of research rather than proof of inefficacy. The effects of lithium have not been studied in the most common rodent tests of impulsivity. Animal tests of impulsivity typically assess impulsivity based on choices the animal makes and protocols for these paradigms require extensive training periods (113, 114).

CONCLUSIONS

Strong evidence exists that lithium reduces the incidence of attempted and completed suicide; these antisuicidal effects of lithium are specific and most likely do not result from its antimanic

and antidepressive actions. However, in spite of more than 30 years of research supporting an antisuicidal effect of lithium, the molecular targets underlying the antisuicidal efficacy of the drug have yet to be identified. These gaps in our knowledge limit the development of novel pharmacological approaches to reduce the incidence of suicide, which could be based on understanding the therapeutic targets of lithium. The results of many studies suggest that measures of aggression and impulsivity are associated with an increased risk of suicide, and that lithium decreases aggression in both humans and rodents. A lithium-induced decrease in impulsivity is less clear; available data suggest a possible decrease in humans and rodents, although data are lacking. Aggression and impulsivity can be readily studied in humans (through both laboratory measures and self-report questionnaires), and tests of both are available for animal studies. Owing to ethical and sampling limitations, suicide is a difficult subject to study, making the endophenotype strategy a valuable approach to investigate the neurobiological underpinnings of suicide.

Among a number of factors, one major limitation for understanding the mechanism by which lithium decreases suicide is the lack of relevant animal models. It is obviously not possible to develop an animal model of suicide that has face validity to the behavior. However, the endophenotype approach, by which quantitative measures of neurobiological function are used to assess and subclassify psychiatric illness, should be useful (49). The mechanisms underlying aggression and impulsivity represent starting points for examining the mechanisms through which lithium may act to decrease suicide.

Much of the research to identify the biological mechanisms involved in aggression and impulsivity has focused on understanding the role of neurotransmitter systems. Serotonin is most often implicated in both aggression and impulsivity. In both humans and nonhuman primates, impulsivity and aggression have been associated with low levels of CSF 5-HIAA, and also reduced serotonin turnover (115). Early studies found an inverse relationship between aggression and serotonin levels; high levels were associated with decreased aggression, and low levels increased aggression in both humans and animals (116). Drugs that act as 5-HT_{1B} receptor agonists lead to a decrease in aggression, and mice that lack the gene for this receptor show increased levels of aggression compared with wild-type mice (116, 117). These knockout mice also show higher levels of impulsivity, as evidenced by shorter attack latencies in the resident intruder test (112). Agonists of the 5-HT_{1A} receptor also lead to a decrease in aggression in animal tests, but this effect is not as specific (and also involves motor changes) (116). Mice that are highly aggressive (derived through a breeding strategy that mates aggressive males with the sisters of aggressive males and nonaggressive males with the sisters of nonaggressive males, while avoiding inbreeding) were shown to have increased 5-HT_{1A} receptor sensitivity (118). The serotonin transporter has also been implicated in aggression, and mice that lack this transporter show lower levels of aggression compared with control mice, and also show longer attack latencies, which indicates lower levels of impulsivity (119).

The effects of lithium on the serotonin system have been studied on multiple levels, including behavioral and cellular. Results from studies are often mixed, with results depending on the region of the brain studied as well as the length of lithium treatment (120). Overall, rodent studies suggest that lithium increases the levels of serotonin as well as its release in specific brain regions (121, 122). Limited or no effect of lithium has been observed on the serotonin transporter following short-term administration to rats, but long-term treatment may lead to increases in several regions of the brain (123). Additionally, lithium treatment of rats appears to have no effect on the density of 5-HT_{1B} receptors in several brain regions (124). Long-term lithium treatment appears to

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

decrease the number of 5-HT_{1A} receptors in rats while differentially affecting behaviors induced by a 5-HT_{1A} agonist in both mice and rats (124–126).

As mentioned, one of the longest-lasting and best-supported theories of both aggression and impulsivity is that low levels of serotonin contribute to these behaviors. The evidence that lithium administration leads to an increase in serotonin as well as complex effects on the serotonin system at multiple levels suggests that lithium may modify aggression through its actions on the serotonin system (120).

The dopamine system is another potential target for lithium's antiaggressive and antiimpulsive effects. Pharmacological treatments that are used to treat aggressive, psychiatrically ill patients are often dopaminergic agents and include both typical and atypical antipsychotics. Haloperidol, for example, has been used for decades in the treatment of psychotic patients who also present with aggressive symptoms, and acts primarily as an antagonist at the D2 dopamine receptors. However, simply decreasing aggression with antipsychotics may not be adequate to decrease suicide, suggesting that lithium acts via a separate mechanism. In mice, antagonists of the D1 and D2 receptors lead to decreased aggression in males, and mice without the long form of the D2 receptor show lower levels of aggression (119). Methods that increase dopamine using pharmacological manipulations tend to increase aggression under certain circumstances in rodents and cats (116). Similarly, mice lacking the enzymes that degrade dopamine as well as norepinephrine [COMT or monoamine oxidase A (MAO-A)] show higher levels of aggression compared with wild-type mice (127, 128). The dopamine transporter is also implicated in aggressive behavior, as mice lacking the transporter show higher levels of aggression than wild-type mice (129). Impulsivity appears to involve the dopaminergic system, as well. Multiple studies in rats have shown that administering D2 or D1/D2 antagonists increases impulsive choice, but D1 antagonist administration does not, suggesting that the D2 receptor plays a role in impulsivity (130).

Lithium has been reported to affect the levels of synaptic dopamine in animal experiments; specifically, long-term administration of lithium decreases dopamine levels or release, an effect that is not generally observed following short-term administration (131–133). Most recently, Ferrie et al. reported that four weeks of lithium administration to rats decreased potassium-evoked dopamine release in the shell of the nucleus accumbens (132). These results persisted even after withdrawal of the drug for three days, suggesting a maintained compensatory effect on dopamine release rather than a direct effect of lithium (132). Lithium also prevents haloperidol-induced dopamine receptor upregulation in rats (134, 135). Multiple studies also indicate that lithium blocks amphetamine-induced hyperactivity in rodents. In 1971, Cox et al. first reported that lithium attenuated stimulant-induced hyperlocomotion in rats (136). This effect was later reported in mice (137–139).

The mechanisms described above are not all-inclusive of the possible targets for lithium's antiaggressive and antiimpulsive actions. Lithium also has many known effects on intracellular signaling pathways (140). Of particular importance may be the effects of lithium on the enzyme glycogen synthase kinase-3 (GSK-3) (141–143). Recent data support a role of GSK-3 in mediating many of the behavioral effects of lithium in rodents, as well as modulating some of the intracellular effects of serotonin and dopamine (144–148). By continuing to define the effects of lithium on various neurotransmitter and cell signaling pathways it may be possible to gain a better understanding of the mechanisms underlying lithium's behavioral effects (98). The behavioral endophenotypes of aggression and impulsivity will be valuable tools for studying mechanisms involved in suicide, and understanding how lithium acts on the neurobiological substrates underlying these behaviors will allow for improved treatment and prevention of suicide.

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

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Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

Annual Review of Pharmacology and Toxicology

Volume 49, 2009

Contents

Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.

Indexes

Errata

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Annu. Rev. Pharmacol. Toxicol. 2009.49:175-198.