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A mathematical theory for temporal changes in tolerance to the behavioral effects of alcohol

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Abstract

Temporal changes in the tolerance to alcohol are rarely discussed. In the behavioral theory proposed here, the rate of increase in tolerance during alcohol exposure is described by linear equations with zero intercept. These equations describe the rate of tolerance growth for acute tolerance, the rate of tolerance growth after alcohol dosing (chronic tolerance), and, for cases in which tolerance has been conditioned, the equations also describe changes in the rate of growth of tolerance when the stimulus set changes. This theory does not explain tolerance acquisition, but may be useful in investigating the physiological basis for tolerance acquisition because it provides numerical values for momentary tolerance that can be compared with concurrent physiological changes. The theory is testable and most of the published behavioral data on non-conditioned tolerance are consistent with the proposed theory. New empirical data on conditioned tolerance are needed to evaluate the proposed theory, and the design for an evaluation is suggested here. Despite its limitations, the theory serves as one example of what a mathematical theory for tolerance might be and may stimulate the development of competing theories with which it could be compared empirically.

Keywords: Acute; Chronic; Conditioned tolerance; Alcohol; Behavior; Ethanol; Linear process; Mathematical theory

Temporal changes in tolerance to alcohol rarely are discussed. In the behavioral theory proposed here, the rate of increase in tolerance during alcohol exposure is described by linear equations with zero intercept. These equations describe the rate of tolerance growth for acute tolerance, the rate of tolerance growth after alcohol dosing (chronic tolerance), and, for cases in which tolerance has been conditioned, the equations also describe changes in the rate of growth of tolerance when the stimulus set changes. Since tolerance changes, "momentary tolerance" must be distinguished from the rate at which tolerance increases.

1. A mathematical theory

A mathematical theory is needed to explain alcohol (ethanol) tolerance accurately. The theory optimally should include mathematical equations that are specific enough to be used to calculate moment-by-moment tolerance magnitudes for empirical data. These equations should include the least complex functional relationships possible so that the structure of the equations can reveal which variable or variables produce changes in tolerance and how the changes come about. The equations also should include variables that explain all factors that affect the magnitude of tolerance.

Many qualitative (non-mathematical) theories can be used to predict a stronger (or weaker) response under one condition than under another (e.g., Baker and Tiffany, 1985; Poulos and Cappell, 1991; Ramsay and Woods, 1997; Siegel, 1975; Solomon and Corbit, 1974). But many theories might be consistent with such a vague prediction and empirical tests may reveal little about the explanatory value of a theory. By contrast, the absolute magnitude of error can be calculated directly from a mathematical theory, and for that reason alternate theories are not necessary in order to assess explanatory power. But theoretical improvements would advance more rapidly if a mathematical theory could be compared with others. The mathematical theory proposed here is not complete, but even in this introductory formulation, the proposed theory, unlike other existing theories, is a workable mathematical model for tolerance to alcohol that can be used with empirical data to describe numerical changes in tolerance.

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2. Tolerance is a physiological event

At its base, alcohol tolerance is a physiological event and a mathematical theory for tolerance should explain physiological data. Eventually such a theory will be developed, but no one has discovered yet how the connection between tolerance and physiological responses can be described by simple equations. Kalant et al. (1971) encountered the difficulty early and, for that reason, proposed the first quantitative behavioral model for acute tolerance. Research since then has revealed more complications at the physiological level. For example, drug administration is recognized to be associated with so many ongoing and elicited effects that it would be difficult to determine which processes are responsible for tolerance growth. "All that can be measured is the integral of all these processes" (Ramsay and Woods, 1997, p 177). Another complication in using physiological measures to describe tolerance is that disputes have developed about which cues, internal and external, actually elicit responses that produce tolerance (cf. Bardo, 2004; Bossert and Shaham, 2004; Bouton, 2004; Kim et al., 1999; McDonald and Siegel, 2004a,b; Stewart, 2004). The criterion for defining tolerance could be narrow (e. g., one physiological measure) or it could be broad (e. g., the global effect of alcohol administration) and different explanations are needed for each. The focus of this paper is on the global behavioral change.

2.1. Mathematical theories that describe the physiology of tolerance have not been successful

No theory based on empirical physiological data exists that can be used to describe alcohol tolerance with mathematical equations. Some theories for alcohol tolerance based on physiological changes do exist that are described as being "quantitative." Peper (2004a, 2004b) introduced a model based on a computer simulation that may be the most sophisticated example, but he described the model as incomplete (Peper, 2004b, p 500). It cannot provide numerical descriptions. He explained also that the model had to be incomplete because of the complexity of the "total response of the organism" (Peper, 2004a, p 488). A mathematical theory for alcohol tolerance based on physiological data is needed, but it does not appear to be feasible now. Behavioral data may be no less complex than physiological data, but a mathematical theory may be possible that is based on recently discovered regularities in behavioral measures of tolerance growth.

2.2. The postulates and corollaries that explain tolerance growth behaviorally

One of the basic strategies in building a mathematical model is to start a priori with a mathematical description based on the most extreme simplifying assumptions. Although this strategy may seem backward, a simple mathematical model will emerge rarely if the model were to be based on an examination of existing empirical data. Theories that were more complex than necessary have been suggested because of such problems as error of sampling and error of measurement. One advantage of this strategy is that empirical tests of simple models provide more information than tests of more complex models. A complex model with many variables can fit almost any data set, but a simple model, especially a linear one, is unforgiving. If the model does not fit the empirical data, the errors are unmistakable.

The mathematical theory introduced here did start with a simplifying assumption that acute tolerance when measured with behavioral data grows at a uniform rate during the time after administration of alcohol. That assumption led to a theory for acute tolerance (Radlow, 1994) that is the basis for the broader theory proposed here. In the theory proposed here one set of postulates and corollaries explains temporal changes in acute tolerance, chronic tolerance, and conditioned tolerance.

Definition 1. Tolerance is the reduction in the effect of a drug at the same blood concentration.

Definition 2. Latent tolerance is the sum of all tolerance that potentially may be expressed in a specified stimulus set and provides a measure of the rate of growth in tolerance with time. It includes initial sensitivity (acute tolerance) and non-conditioned (chronic) tolerance that will be expressed any time alcohol is administered. It includes also any conditioned tolerance that has been acquired. Conditioned tolerance will be expressed fully in a stimulus set identical to that in which the conditioned tolerance was acquired. In other stimulus sets, conditioned tolerance will not be expressed fully and the magnitude of latent tolerance will be smaller than the potential maximum.

Definition 3. Momentary tolerance is the tolerance magnitude at a specified time and is determined by the rate of growth (latent tolerance) and the elapsed time after alcohol administration.

Postulate 1. Each organism has latent tolerance, part or all of which can be expressed when alcohol is administered.

Postulate 2. Momentary tolerance has a value of zero when alcohol is administered.

Postulate 3. Momentary tolerance increases after alcohol administration at a uniform rate with respect to time if the stimulus set is unchanged during the session, a linear growth,

Postulate 4. Latent tolerance is the rate of momentary tolerance growth, the slope of the tolerance line.

Postulate 5. Momentary tolerance increases at a rate that is independent of momentary blood alcohol concentration (BAC).

Postulate 6. If tolerance had been conditioned and the stimulus set were to change during the experiment, latent tolerance would change at the same time and momentary tolerance would increase at a different uniform rate (Postulate 3).

Corollary 1. A more reliable estimate of tolerance magnitude can be obtained with the slope of the tolerance line than with a single measurement because tolerance is changing with time (Postulates 3 and 4).

Corollary 2. Latent tolerance does not change during a session in which alcohol has been administered (Postulates 3 and 4). If

momentary tolerance increases at a uniform rate in the same stimulus set, latent tolerance must be constant.

Corollary 3. Increases in latent tolerance may occur following any session in which alcohol had been administered. Decreases in latent tolerance may occur after prolonged periods of abstinence. Corollary 3 follows from Corollary 2. If latent tolerance does not change during a session in which alcohol has been administered, any changes in tolerance observed afterward must be the result of alcohol dosing during the session, of alcohol dosing after the session, of a period of abstinence, or of some combination of these treatments.

2.3. Application of the theory to acute tolerance

When alcohol is administered to an alcohol-naive organism, the tolerance observed (initial tolerance) is called "acute tolerance." Mellanby (1919) was the first to describe an increase in tolerance with time, but he did not discuss the rate of tolerance growth. Curiously, his discovery has been described as "acute tolerance" consistently although his subjects, four dogs, certainly were not alcohol naive. They were the subjects in a long series of studies reported in Mellanby's monograph. Experiments with human volunteers also are described as acute tolerance consistently although these volunteers never are alcohol naive. This blurring of the distinction between acute and chronic tolerance may not be important, however, because in the theory proposed here the same postulates apply to both.

Momentary tolerance has a value of zero when alcohol is administered and increases at a uniform rate with respect to time (Postulates 2 and 3), defining a process that can be described by Eq. (1), the general equation for a straight line with a zero intercept.

$$Y = mT. \tag{1}$$

The variables "T" and "Y" are the elapsed time after alcohol administration and the momentary tolerance, respectively. The constant "m" is the slope of the tolerance line.

Every acute tolerance line must have this form to be consistent with Postulates 2 and 3. Only the slope of the line can be different. If acute tolerance is strong, the value for "m" would be relatively large and the slope will be steep. If acute tolerance is weaker, the value for "m" would be smaller and the slope will be less steep. If no acute tolerance develops at all, the value for "m" would be zero and the acute tolerance line would fall on the abscissa. These slopes could be calculated from empirical data. A line labeled "acute tolerance" is shown in Fig. 1 for a comparison with other applications of the theory.

2.4. Application of the theory to chronic tolerance

Chronic tolerance is the diminished effect of a drug after administration of that drug on one or more previous occasions. Since Postulates 2 and 3 contain no distinction between acute and chronic tolerance, momentary tolerance also has a value of zero in chronic tolerance studies and increases at a uniform rate. Latent tolerance should be greater than on previous alcohol administrations because it would include both initial and acquired tolerance (Definition 2). And, because latent tolerance has increased, the rate of tolerance growth would increase (Definition 3 and Postulate 4). The increase in the rate of tolerance growth would be manifested in a steeper slope for the tolerance line than previously for the same individual or group of individuals. For these reasons, the equation that applied to acute tolerance, $Y=mT$ (but with a larger value for "m"), applies also to chronic tolerance. And, as with acute tolerance, the slope for the chronic tolerance line could be calculated from empirical data. A line with a relatively steep slope labeled "chronic tolerance" is shown in Fig. 1 for a comparison with other applications of the theory.

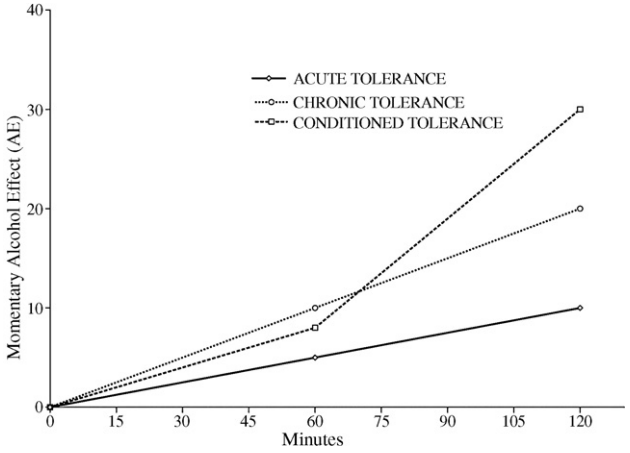

Fig. 1. The theoretical representation of acute, chronic, and conditioned tolerance.

A relationship between acute and chronic tolerance had been suggested (Kalant et al., 1971, 1978; Littleton, 1980), but none suggested any specific rate of change. No specific rate of change in tolerance could have been verified then because no theory had been published to define what should be measured. Several years later, changes in tolerance could be measured by changes in the slope of the underlying acute tolerance line (cf. Radlow, 1994). In another paper (Radlow, 1993), a theory was proposed to explain quantitative changes in latent tolerance after multiple sessions (chronic tolerance). These ideas are formalized in the present theory with Postulates 1–5. The effect of conditioned tolerance is introduced in the theory through Postulate 6.

2.5. Application of the theory to conditioned tolerance

Momentary tolerance increases at a uniform rate if the stimulus set is unchanged (Postulate 3), but if the stimulus set were to change and tolerance had been conditioned, latent tolerance would change at the same time (Postulate 6) and momentary tolerance would increase at a different but uniform rate (Postulate 3). A segmented line with two straight segments would be created by a change in stimulus set during an experiment. If the stimulus set were more like the stimulus set

during conditioning, the second segment of the line would be steeper than the first segment of the line; otherwise it would be less steep. Eq. (2) provides a numerical description of the effects of changes in the stimulus set at time t on momentary tolerance that had been conditioned earlier.

$$(Y-y) = m^*(T-t) \quad (2)$$

The variables "T" and "Y" are the elapsed time after alcohol administration and the momentary tolerance, as before. The constants "t" and "y" are the time and the momentary tolerance magnitude at the time the stimulus set changed. Eq. (2) describes a line that starts where the first segment of the line ended (y, t), but continues with a different slope, m^*.

Fig. 1 illustrates the application of the theory to momentary tolerance growth. As noted before, the lines labeled "acute tolerance" and "chronic tolerance" are examples of uniform growth in momentary tolerance. The latter is steeper because of acquired latent tolerance. To illustrate how the effect of changes in stimulus set is conceptualized in the proposed theory, a segmented line labeled "conditioned tolerance," is shown in Fig. 1 that changes slope at 60 min (when the stimulus set changed). In this example, the stimulus set is assumed to have changed to a stimulus set more like the one during conditioning, eliciting a stronger conditioned tolerance response. The two slopes in this segmented line could be calculated from the empirical data.

2.6. Methodological issues in the evaluation of the proposed theory

The basic rationale for the assessment of tolerance in all experiments is the same: If tolerance did not exist, alcohol effect (AE) for an organism always would be proportional to momentary BAC. If tolerance did exist as hypothesized in the proposed theory (Postulate 3), momentary AE should be progressively weaker than proportional to momentary BAC. Testing that hypothesis can be confusing because at least three kinds of method have been used, and momentary tolerance must be inferred from momentary AE differently for each. With the Type 1 method, BAC is held constant and increases in momentary tolerance are inferred from improved performance with time. With the Type 2 method, task difficulty (or score) is held constant and increases in momentary tolerance are inferred from the ability to perform the task with increased BAC as time progressed. And, with the Type 3 method, neither BAC nor task difficulty is held constant and some mathematical procedure must be used to calculate that part of the change in momentary AE that does not result from changes in BAC. To minimize confusion about what is being measured and why, the studies cited here will be grouped by these three methods. Since grouping the experiments by method separates the empirical evidence relating to each postulate, results will be summarized in the Discussion and Conclusions section. No distinction is needed for experiments that apply primarily to acute, chronic, or conditioned tolerance because the postulates apply to all of them.

2.7. Empirical evidence in which the Type 1 method is used

Constant BAC is very difficult to achieve, especially so with humans because most volunteers accept only oral consumption. But the Kaplan et al. (1985) method qualifies as Type 1 because they were able to keep human volunteer BAC approximately equal (80–100 mg/dl measured by blood samples from an indwelling IV) during 7 trials over a period of 6 h. On their cognitive task, short-term word recall (their measure of AE) had declined sharply at 0.67 h after consumption of ethanol (0.9 g/kg lean body mass) as BAC rose from 0 to approximately 90 mg/dl. On subsequent trials (at 2, 3, 4, 5, and 6 h after consumption) at which BAC was held constant, Kaplan et al. show in their Fig. 1a that performance improved (momentary tolerance grew) at a uniform rate per unit time, consistent with Postulate 3. For the other tasks (body sway, manual tracking, and intoxication/sedation scores), neither improvement nor decline was found during the 6 h (no alcohol tolerance), a result that has no bearing on the validity of Postulate 3.

Le and Kalant (1992) administered ethanol (1.8 g/kg IP) to 9 rats in one experiment and 2.2 g/kg to 9 rats in a second experiment, in each experiment using a moving-belt task in which a rat was tested once and sacrificed (cf. LeBlanc et al., 1975). The method qualifies as Type 1 because tested BAC was approximately equal at each trial time in both experiments. Acute tolerance increased at a uniform rate with respect to time in both experiments, a result that is consistent with Postulate 3. In each of the two experiments, Le and Kalant studied an additional group of 9 rats with a different procedure. Instead of sacrificing each rat at the end of one trial, rats were tested on each of the 5 trials of the session. With this intoxicated practice procedure, acute tolerance increased at an accelerated rate (faster than linear), a result that is not consistent with Postulate 3. Other studies with intoxicated practice that are discussed in this paper show linear, not faster than linear, growth in tolerance, including LeBlanc et al. (1975), Grieve et al. (1979), Rimmele (1984), Kaplan (1985), Radlow (1994), Wu et al. (2001), and Tampier and Quintanilla (2002). Another of these intoxicated practice studies that showed linear growth in tolerance used the same task as Le and Kalant, the same animals (rats), and was conducted in the same laboratory (Khanna et al., 2002). Further study will be required to explain the inconsistency.

Tampier and Quintanilla (2002) administered ethanol (2.3 g/kg IP) to 15 rats in each of four groups using the tilted-plane task. The method qualifies as Type 1 because tested BAC was approximately equal for the duration of the experiment both for the first and for the second experimental session. Their results are consistent with Postulate 4 because the tolerance line increased in slope on the second session with increased alcohol dosing between the two sessions (free choice of 10% ethanol or water for 15 days). They also reported that the tolerance line, based on 3 data points, was straight on the first session, a result consistent with Postulate 3, but Postulate 3 could not be tested with data from the second session because AE fell to zero so rapidly that the tolerance line was based on only two points. Tampier and Quintanilla data also could not be used to evaluate

Postulate 2 because the AE score at zero BAC was a non-zero performance measure rather than a measure of impairment.

2.8. Empirical evidence in which the Type 2 method is used

LeBlanc et al. (1975) used a complex method that can be treated as a method of Type 2 (task difficulty, or score, is held constant) because rats in the three groups that were tested at different times after alcohol administration had approximately equal error scores on a moving-belt task. Sixty rats in three groups of 20 were tested either at 10, 30, or 60 min after ethanol administration. Rats in each of the three groups were tested at 10 different doses (pairs of rats in each group received the same dose of ethanol) that averaged 1.5, 1.9, or 2.3 g/kg respectively. Each of the 60 rats was tested once in this experiment to insure that if acute tolerance were found, practice effect could be ruled out. A plot of brain ethanol level (abscissa) against error score (ordinate) in their Fig. 1 showed that the three lines for the three test groups were parallel to each other. (The data formed three lines each of which tilted to the right because 10 different dose levels were used for each group, and individual rats in each group with a slightly higher dose had slightly higher brain ethanol concentration and slightly higher error score.) LeBlanc et al. concluded, "The parallel shift of regression lines (Fig. 1) constitutes by definition the evidence of tolerance (Kalant et al., 1971)." The rate at which momentary tolerance was rising could be found by plotting against time the average brain ethanol level for each of the three groups (estimated from the LeBlanc et al. Fig. 1). The figure would show a uniform increase in BAC for performance with equal error scores (the three points would form a rising straight line), a result that is consistent with Postulate 3.

LeBlanc et al. (1975) evidence also was consistent with Postulate 5 because, despite the rise in brain ethanol concentration, momentary tolerance increased at a uniform rate with respect to time. If momentary tolerance growth had been BAC dependent, momentary tolerance would have increased at a progressively faster rate (faster than linear) as brain ethanol concentrations increased.

Grieve et al. (1979) also used the Type 2 method (a righting reflex task with a pass/fail criterion). Each of 4 C57BL mice was administered an ethanol priming dose of approximately 2.5 g/kg IP and BAC was increased afterward in an inhalation chamber. Each time a mouse lost righting reflex (inability to right within 30 s), the mouse was withdrawn from the chamber and BAC was determined. Data for mice could not be averaged because each mouse was tested by a performance criterion (was able to right itself) that would occur at different times for each of the mice. In their Fig. 3, BAC was plotted against the time at which a mouse lost righting reflex and the points for each mouse form an almost straight line, a result consistent with Postulate 3. Extrapolating backward, each of the lines also intersects the abscissa close to the origin, results that are consistent with Postulate 2. Results for the C57 strain also are consistent with Postulate 5 because, despite the rise in BAC, momentary tolerance increased at a uniform rate with respect to time. As with the LeBlanc et al. (1975) data, if acute tolerance growth had been BAC dependent, momentary tolerance would have increased at a progressively faster rate (faster than linear) as BAC rose in the alcohol-infused inhalation chamber.

The data displayed by Grieve et al. in their Fig. 3 for individual TO Swiss mice are more variable than those for the C57 strain, show less acute tolerance, and are less clearly indicative of linear acute tolerance growth. Whether or not these results are consistent with Postulates 2 and 3 is unclear because of variability in the data and, as with the much more reliable C57 data, data for TO Swiss mice could not be averaged because each mouse was tested by a performance criterion at different times. Data for DBA2 mice show no appearance of acute tolerance development. Failure to develop momentary tolerance is not inconsistent with Postulate 3.

Wu et al. (2001) used a Type 2 method (a stationary rod task with a pass/fail criterion). In the first session of the study (acute tolerance), mice were tested for stationary rod ataxia after they were administered ethanol (1.75 g/kg IP). The same mice were dosed heavily with ethanol (3.5 g/kg IP twice daily for the six days between the two sessions), and then they were tested in a second session with the same procedure as for the first. Stationary rod ataxia on the initial trial of the second session occurred at the same BAC value as for the first. These results are consistent with Postulate 2. They also found that the tolerance line increased in slope on the second session, a result consistent with Postulate 4. Postulate 3 could not be tested because the slope for each line was calculated from only two points.

Wu et al. (2001) obtained a different result in another condition of their experiment. Mice of the same genetic line as in the other study were tested with an intersession dose of 3.0 g/kg instead of 3.5 g/kg, but otherwise with exactly the same procedure. With this lower intersession dose, performance during Session 2 showed no growth in functional tolerance above performance during Session 1. This result indicates that increases in chronic tolerance may appear only with administration of an intersession dose that exceeds a threshold value.

2.9. Empirical evidence in which the Type 3 method is used

With the Type 3 method, neither BAC nor task difficultly is held constant and some mathematical procedure must be used to calculate that part of the change in momentary alcohol effect (AE) that does not result from changes in BAC. Two very similar procedures have been used that employ the same principle. Procedure 1 is a direct application of the theory that a tolerance line exists that starts at zero and is a measure of the amount of tolerance increase per unit time. But the calculation of the underlying acute tolerance function is quite complex. Procedure 2 uses much simpler and more direct calculation to find the rate of change in tolerance but not the tolerance line itself. In both Procedures 1 and 2, a data transformation is needed to evaluate the proposed theory. A data transformation is needed because the use of raw data in units both of BAC and of AE would violate a principle of "dimensional analysis," or what is popularly called "subtracting apples from oranges." If you were to subtract BAC (apples) from AE (oranges), the number you would get would be meaningless. A mathematical transformation is needed to obtain "dimension-free" numbers so that the subtraction can be valid.

Dimension free numbers could be found if percentages of the maximum (%max) value were calculated for each of the variables. For example, if a BAC of 0.08% at 90 min were the maximum for a session, the percent maximum score for a BAC of 0.06% at 60 min would be 0.75. The number "0.75" is a pure ratio and, therefore, is dimension free. The transformation is obtained at a price, because the absolute magnitude of the raw scores is lost both in Procedure 1 and in Procedure 2, and absolute magnitudes may be important for some purposes. Raw empirical scores and the percent maximum scores derived from them will be presented as part of an illustration of how Type 3 method can be applied. Type 1 or Type 2 method do not require a data transformation, but Type 3, despite its limitations, is useful when no other method can be used.

Procedure 1. Alcohol effect (AE) would be proportional momentary BAC scores if momentary tolerance did not exist. But, if Postulates 2 and 3 were correct, there must be a tolerance line, starting at zero, that provides a pure measure of momentary tolerance growth. The proposed theory would be supported if when the values on this line are subtracted from the corresponding values on the BAC %max curve, the subtractions produce accurately measures that are proportional to momentary AE. Procedure 1 requires a complex calculation to find the slope for the correct tolerance line.

The procedure to calculate the slope of the tolerance line will be described first and then illustrated with empirical data. In practice, a computer program makes all of these calculations painlessly. First, the data must be made dimension free. Then the logic of the procedure requires starting from the end and working backward. Begin with a line that starts at zero (to be consistent with Postulates 2 and 3) that has a very shallow slope. If that were the correct acute tolerance line, subtracting points on that line from the BAC %max curve should result in a curve (theoretical AE %max) that matches the empirical AE %max curve because momentary AE is the result of the impairment from momentary BAC minus the reduction in impairment from momentary tolerance. The correct acute tolerance line is the one that produces the minimal squared error when it is used to calculate the theoretical value for AE. Try other lines with small increments in slope. For each line, points on the line are subtracted from the corresponding points on the empirical BAC %max curve. The subtraction results in numbers that are no longer on a percent maximum scale (no number will be 100%) and the percent maximum scale must be restored. These restored percent maximum values define the "theoretical AE curve." For each of the lines that is analyzed, the final step is to compare each data point on the empirical AE %max curve with the corresponding point on the theoretical AE %max curve. Sum the squares of all the errors. A tolerance line is selected by this procedure that results in the smallest sum of squared errors. That sum may be small and it may be large. If the sum of squared errors is small, the theoretical AE %max curve provides a good fit to the empirical AE %max curve, a result consistent with Postulate 3.

This process may appear to be circular because all of the empirical data (BAC %max and AE %max) have been used in some way by the method to select the best-fit tolerance line. But it is not circular. Empirical AE %max values are not used in any way to calculate the form of the theoretical AE %max values. This method does not prove anything by itself. The test of Postulate 3 is whether or not the fit is accurate. An accurate fit is possible only if the underlying growth in momentary tolerance were linear. If the true function were non-linear, the calculated curve would fit the empirical one only at points of crossover and the sum of the squared errors would be large.

The method for Procedure 1 is illustrated here with empirical data from a study with 24 human volunteers (Rimmele, 1984). Magnitude estimation, a psychophysical scale developed by Ekman et al. (1963) and used in many human studies, was used to measure AE. Table 1 shows in successive columns the time after ethanol consumption, the raw BAC and AE scores, and the corresponding percent maximum scores for BAC and AE. The acute tolerance (AT) line, in the next column, was calculated by the procedure that produced the smallest squared error as described above and had a slope of 9.98 degrees. The BAC-AT values, in the next column, were found by subtracting the corresponding values on the AT line from the BAC %max values. Since all values in the BAC-AT column are based on % max scores but below 100%, the percent maximum scale was restored in the last column. This column, labeled "Theor AE," contains the predicted or theoretical AE %max values. If the proposed theory were correct, these theoretical AE %max scores should match closely the empirical AE %max scores.

The raw scores are in different units and cannot be shown in a figure meaningfully, but Fig. 2 shows the empirical BAC and AE values as %max scores. The AT line selected by the procedure described above is shown along with the theoretical value for AE (the restored percent magnitude values in Table 1) that was calculated with values from the AT line and BAC. The theoretical values for AE %max clearly are almost exactly the same as the empirical AE %max scores, with a Pearson product moment correlation of 0.9995 between predicted and empirical

Table 1
The data used to calculate theoretical alcohol effect (Theor AE %max) for an experiment in which alcohol effect results both from changes in momentary BAC and from changes in momentary tolerance with time

Min	Raw BAC	Raw AE	BAC %	AE %	AT line	BAC-AT	Theor AE
0	0	0.00	0.00	0.00	0.00	0.00	0.00
30	0.093	13.61	81.40	84.50	5.28	76.12	86.02
42	0.106	15.40	92.70	95.59	7.39	85.31	96.39
54	0.112	16.11	98.00	100.00	9.50	88.50	100.00
66	0.114	15.89	100.00	98.70	11.62	88.38	99.87
78	0.112	15.38	97.70	95.40	13.73	83.97	94.89
90	0.112	15.00	97.80	93.10	15.84	81.96	92.61
102	0.11	14.00	96.40	86.90	17.95	78.45	88.65
114	0.106	13.34	92.90	82.80	20.06	72.84	82.31
126	0.104	12.59	91.10	78.20	22.17	68.93	77.88
138	0.101	11.72	88.80	72.70	24.29	64.51	72.90

The procedure is described in the text as Type 3 method, Procedure 1. The slope of the acute tolerance (AT) line is the rate at which tolerance increases with time. Momentary tolerance is the value on the AT line at each trial time. Theor AE % max is compared with empirical AE %max to test he theory. The empirical data are from Rimmele (1984). The slope for the calculated acute tolerance line is 9.98 degrees.

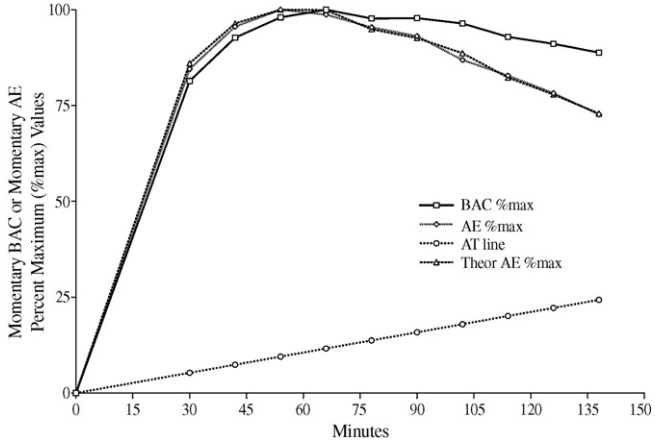

Fig. 2. A comparison of the empirical alcohol effect (AE %max) data with the theoretical AE (Theor AE %max) data. The nearly perfect overlap of these two curves is consistent with the theory. The procedure employed to calculate the values in this figure is described in the text as Type 3 method, Procedure 1. The slope of the acute tolerance (AT) line is the rate at which tolerance increases with time. The decrease in both AE %max curves relative to the BAC %max curve is the result of the growth in tolerance with time. Empirical data are from Rimmele (1984).

data points. This close concordance suggests that the underlying momentary tolerance must have started at zero and grown at a uniform rate per unit time because, as explained earlier, otherwise the errors would have been large. These results, therefore, are consistent with Postulates 2 and 3. The finding of a straight acute tolerance line despite BAC levels that rise and fall also is consistent with Postulate 4.

Procedure 1 constrains the tolerance line to start at zero. The principal reason for this constraint is that Postulate 2 requires the line to start at zero; using the constraint consequently provides a better test of the theory. If Postulate 2 were not correct, error would be introduced and the tolerance line calculated by this procedure would result in a less accurate fit to the empirical %max AE curve. The close fit obtained with the Rimmele, 1984) empirical data is consistent with the zero start (Postulate 2) and other characteristics of the theory. In this experiment, empirical evidence also justifies the constraint of a zero start. At time zero, alcohol had not yet been administered and the measured BAC was zero. AE also was measured and had a value of zero. Other studies described earlier (Grieve et al., 1979; Wu et al., 2001) also provide direct empirical evidence consistent with a zero start.

Radlow (1994) also used Procedure 1 with empirical data from a study by Radlow and Hurst (1985). Forty human volunteers participated. Magnitude estimation was used to measure AE. Ethanol was consumed with a dose of 1.0 g/k. Employing the procedure described above, the AT line that resulted in the smallest squared error had a slope of 10.6°. The correlation between predicted AE %max and empirical AE %max data points was 0.993 in this experiment, a close concordance that provides evidence consistent with Postulates 2–5.

Procedure 2. Khanna et al. (2002) developed a procedure that was based on the same principle used for Procedure 1. They said, "The basic concept is that in the absence of acute tolerance, the BAC and the effect should follow parallel curves over time; the increasing discrepancy between BAC and effect is therefore the measure of tolerance (Radlow, 1994)." This discrepancy was called an "impairment score."

The Khanna et al. procedure is simpler than Procedure 1 because it does not require complex calculations to find the acute tolerance line. It starts the same way as Procedure 1 with conversion to percent maximum scores to obtain scores that are dimension free. Then, when the percent maximum impairment score is subtracted from the percent maximum BAC score, an "output function" score is obtained that is proportional to changes in tolerance but is not the tolerance line. The logic of this procedure is that if the output function were linear, the underlying increase in tolerance would be linear. This method was applied in two experiments to 36 rats that were administered eight different doses of ethanol IP. AE was measured by performance on a tilted plane. They concluded that the output functions were linear, a result that is consistent with Postulate 3. But the validity of Postulate 2 could not be evaluated and would have to be tested in another way because the output function is not a tolerance line and only the tolerance line is postulated to start at zero.

Khanna et al. (2002) designed this study to determine whether or not momentary tolerance growth was independent of BAC (Postulate 5). Four groups of rats in one experiment were administered ethanol in higher doses of 2.5, 2.7, 3.0 and 3.3 g/kg and three groups of rats in another experiment were administered ethanol in lower doses of 1.9, 2.3 and 2.8 g/kg. They found that the effect of dose was not significant and that the output functions were straight for each of groups and concluded (on p. 296) that their data support both a linear increase in momentary tolerance (Postulate 3) and "Radlow's (1994) hypothesis that growth of acute tolerance is time dependent but dose independent." These outcomes are consistent with Postulates 3 and 5.

Procedure 2, introduced by Khanna et al. (2002), could be applied also to the Rimmele (1984) data that were analyzed earlier by Procedure 1. When this relatively simple procedure is applied to the data in Table 1, a linear fit results in a line ($Y=0.142X-6.402$) that closely approximates the rescaled empirical data (the "output function," BAC %max − AE %max) and shows in another way that tolerance growth is linear (Postulate 3). The Y intercept is not zero, a result that would not be expected because this is an "output function," not a tolerance line.

Procedures 1 and 2 are based on the same principle, but each has advantages and disadvantages. The advantage in using Procedure 2 is that it is much simpler computationally, and like Procedure 1 still can be used to test Postulate 3 (the linearity postulate). The disadvantage in using Procedure 2 is that it results in an "output function" that provides less information than an acute tolerance line. The first advantage in using Procedure 1 is that by calculating the acute tolerance line it is possible to test Postulate 2 (Momentary Tolerance starts at zero). The second advantage in using Procedure 1 is that the slope of the calculated tolerance line provides a direct measure

for the rate of tolerance growth. The disadvantage in using Procedure 1 is that it requires complex computation.

The method used by Kalant et al. (1978) also can be classified as Type 3 because performance level on a moving-belt task certainly changed and BAC probably changed; values were not reported and rats were administered a single dose of ethanol IP. Neither Procedure 1 nor Procedure 2 can be applied because BAC is changing but not reported; the underlying tolerance growth cannot be calculated. Postulate 3 cannot be evaluated because linearity of tolerance growth cannot be verified, but evidence presented does bear on the validity of some postulates. Kalant et al. stated that "… tolerance developed more rapidly during cycle 2 than during cycle 1 in Groups 1–4, *regardless of which treatment they had received during cycle 1*." (Italics were used by the authors.) This result, which suggests that chronic tolerance is an acceleration of acute tolerance, is consistent with Postulate 4. They also stated that "It is important to note that the acceleration of tolerance was not due to summation of newly developed tolerance with that remaining from the first cycle, since the first alcohol exposure in the second and later cycles of each experiment produced the same effect as in the initial test of the first cycle. Thus, it is not tolerance that is carried over between cycles, but an enhanced ability to develop it." This result is consistent with Postulate 2.

2.10. Assessment of the theory for conditioned tolerance

Postulate 6 is the explanation for changes in the rate of momentary tolerance growth when the stimulus set is changed and some part of latent tolerance has been conditioned. This postulate is testable, but no empirical data are available yet by which it could be tested. The theory could be tested empirically with a design that begins with conditioning tolerance in two randomly assigned groups of subjects. Test the first group on a behavioral task while exposed to the stimulus set that would be expected to elicit the maximum conditioned tolerance (the original stimulus set during conditioning), and later during that same session change the stimulus set to reduce the tolerance elicited by the stimulus set. If Postulate 6 were correct, the first part of the segmented tolerance line for group 1 would have a steeper slope than the second segment of the line. Postulate 6 could be tested in another way with the second group. Use the same procedure, but reverse the order of the presentation of stimulus sets. If Postulate 6 were correct, the first part of the segmented tolerance line for group 2 would have a shallower slope than the second segment of the line. This latter case is illustrated in Fig. 1, in which the slope of the first segment has a value intermediate to the slopes for the acute tolerance and the chronic tolerance lines. The second segment of the line has a slope that is steeper than any of the other lines. The existence of this theory may encourage an empirical test of Postulate 6 either with the experimental design suggested or with another design.

3. Discussion and conclusions

Three types of method that have been used in the literature to study tolerance, and the results obtained were described for each method because each required a different rationale to evaluate the validity of the postulates. The results are recompiled here separately for each postulate to provide a systematic evaluation of the theory.

No test of Postulate 1 was discussed because latent tolerance is implicit in the concept of conditioned tolerance.

Data consistent with Postulate 2 were reported for rats by Kalant et al. (1978), for mice by Wu et al. (2001), and for humans by Rimmele (1984) and by Radlow, 1994. Data consistent with Postulate 2 were reported for C57 mice by Grieve et al. (1979), but whether data for TO Swiss mice are consistent or not with Postulate 2 is unclear because of variability in the data. Grieve et al. data for DBA mice are not inconsistent with Postulate 2 because they show no growth in acute tolerance. Other data (LeBlanc et al., 1975; Le and Kalant, 1992; Kaplan et al. 1985; Tampier and Quintanilla (2002); Khanna et al., 2002) could not be used to evaluate Postulate 2 because the AE score at zero BAC was a non-zero performance measure rather than a measure of impairment. Most data reviewed here are consistent with Postulate 2.

Data consistent with Postulate 3 were reported for rats by LeBlanc et al. (1975), Le and Kalant (1992) for a single-trial method, Khanna et al. (2002), and Tampier and Quintanilla (2002). Data consistent with Postulate 3 were reported for each of the C57BL mice in the study by Grieve et al. (1979). Data consistent with Postulate 3 were reported for humans by Kaplan et al. (1985), Rimmele (1984) and Radlow (1994). Data reported by Kalant et al. (1978) and by Wu et al. (2001) are neither consistent nor inconsistent with Postulate 3 because linearity of tolerance growth cannot be evaluated. The method used by Kalant et al. (1978) does not report or control BAC and the method used by Wu et al. determines the slope of tolerance lines by two points.

As with Postulate 2, whether or not the highly variable data for TO Swiss mice (Grieve et al., 1979) are consistent with Postulate 3 is unclear. Le and Kalant (1992) reported data that were inconsistent with Postulate 3 for the multiple trials condition. But this Le and Kalant finding is inconsistent with several other intoxicated practice experiments, as noted previously, including a later study from the same laboratory with the same animals (rats) but with a different task. Most data reviewed here are consistent with Postulate 3, but some data are ambiguous, and one study reported data that were inconsistent with the postulate.

Data consistent with Postulate 4 were reported for rats by Kalant et al. (1978) and by Tampier and Quintanilla (2002). Data consistent with Postulate 4 were reported for mice by Wu et al. (2001). Postulate 4 applies only to multiple session experiments (chronic tolerance). Other studies cited in this paper (LeBlanc et al., 1975; Grieve et al., 1979; Rimmele, 1984; Kaplan et al. 1985); Le and Kalant, 1992; Radlow, 1994; Khanna et al., 2002) were single session studies and did not bear on the validity of Postulate 4. All data reviewed here that bear on its validity have been consistent with Postulate 4.

Data consistent with Postulate 5 were reported for rats by LeBlanc et al. (1975) and by Khanna et al. (2002), for mice by Grieve et al. (1979), and for humans in this paper with data by Rimmele (1984) and by Radlow (1994). Other studies (Kalant

et al., 1978; Kaplan et al. 1985; Le and Kalant, 1992; Wu et al., 2001; Tampier and Quintanilla, 2002) were neither consistent nor inconsistent with Postulate 5 either because BAC was constant or because linearity of tolerance growth could not be evaluated. All data reviewed here that bear on its validity have been consistent with Postulate 5.

No data bearing on the validity of Postulate 6 have been reported, but an experimental design is suggested in this paper that could provide the data necessary.

3.1. Limitations of the proposed theory

One challenge to the generality of the theory is that many studies have demonstrated cognitive influences on growth in momentary tolerance, with the data from studies on "expectancy" by Vogel-Sprott and her colleagues most similar to the time-based data described here. Their studies have shown for example that momentary tolerance increased when human volunteers were provided with informational feedback about the accuracy of their performance on a psychomotor task in each of three successive sessions, but in another condition that lacked this informational feedback, momentary tolerance did not grow at all although dosage and all other conditions save cognitive feedback were the same (Sdao-Jarvie and Vogel-Sprott, 1991). In another study, tolerance was shown to grow in human volunteers for a psychomotor task after mental rehearsal of their performance, and the magnitude of the tolerance acquired was comparable to another group that had physical practice (Sdao-Jarvie and Vogel-Sprott, 1992). These results appear to be consistent only with an explanation based on cognitive factors. In its present form, the proposed theory cannot explain these cognitive factors.

The principal limitation of the proposed theory is that it explains how momentary tolerance changes with time and with changes in stimulus set, but does not explain the process by which latent tolerance is acquired either because of alcohol dosing or because of conditioning. Another aspect of this limitation is that threshold effects in intersession ethanol dosage may determine whether or not latent tolerance will grow (cf. Wu et al., 2001). A satisfactory explanation of latent tolerance acquisition could be behavioral (specified conditions or operations that result in measurable changes in latent tolerance) or it could be physiological. Another limitation of the proposed theory is that some tasks performed by the same subjects result in different rates of momentary tolerance growth than others, and that some strains and species differ in how they develop tolerance. The proposed behavioral theory can explain some of these differences by assigning tolerance lines of different slopes, including zero, to different tasks and species, and the behavioral explanation could be expanded to minimize these limitations. A mathematical formulation for a physiological theory would provide a more satisfying explanation because most of these differences have a physiological basis. No mathematical theory of that kind exists yet, but the proposed theory may be useful in developing new ways to study the underlying physiological processes of tolerance. One suggestion is that because the theory provides numerical values for changes in momentary tolerance with time of exposure to alcohol, these changes may help to identify the most important concurrent physiological changes.

Most of the published data are consistent with the postulates of the proposed theory, but the data set is relatively small. More data are needed, especially to test Postulate 6, the postulate about changes in stimulus set. Despite its limitations, the theory serves as one example of what a mathematical theory for tolerance might be and may stimulate the development of competing theories with which it could be compared empirically.

References

Baker TB, Tiffany ST. Morphine tolerance as habituation. Psychol Rev 1985;92:78-108.

Bardo MT. On the nature of the intra-administration unconditioned stimulus: comment on McDonald and Siegel. Exp Clin Psychopharmacol 2004;12:12–4.

Bossert JM, Shaham Y. Drug onset cues, conditioned withdrawal, and drug relapse: comment on McDonald and Siegel. Exp Clin Psychopharmacol 2004;12:15–7.

Bouton ME. A general role for early onset cues and intra-event learning: comment on McDonald and Siegel. Exp Clin Psychopharmacol 2004;12:18–9.

Ekman G, Frankenhaeuser M, Goldberg L, Bjerver K, Jarpe G, Myrsten A-L. Effects of alcohol intake on subjective and objective variables over a five-hour period. Psychopharmacologia 1963;4:28–38.

Grieve SJ, Griffiths PJ, Littleton JM. Genetic influences on the rate of development of ethanol tolerance and the ethanol physical withdrawal syndrome in mice. Drug Alcohol Depend 1979;4:77–86.

Kalant H, LeBlanc AE, Gibbins RJ. Tolerance to, and dependence on, some non-opiate psychotropic drugs. Pharmacol Rev 1971;23:135–91.

Kalant H, LeBlanc AE, Gibbins RJ, Wilson A. Accelerated development of tolerance during repeated cycles of ethanol exposure. Psychopharmacology 1978;60:59–65.

Kaplan HL, Sellers EM, Hamilton C, Naranjo CA, Dorian P. Is there acute tolerance to alcohol at steady state? J Stud Alcohol 1985;46:253–6.

Khanna JM, Morato GS, Kalant H. Effect of NMDA antagonists, an NMDA agonist, and serotonin depletion on acute tolerance to ethanol. Pharmacol Biochem Behav 2002;72:291–8.

Kim JA, Siegel S, Patenall VRA. Drug onset cues as signals: intraadministration associations and tolerance. Journal of Experimental Psychology. Anim Behav Process 1999;25:491–504.

Le AD, Kalant H. Influence of intoxicated practice on the development of acute tolerance to the motor impairment effect of ethanol. Psychopharmacology 1992;106:572–6.

LeBlanc AE, Kalant H, Gibbins RJ. Acute tolerance to ethanol in the rat. Psychopharmacologia 1975;41:43–6.

Littleton JM. The assessment of rapid tolerance to ethanol. In: Rigter H, Crabbe JC, editors. Alcohol tolerance and dependence. Amsterdam: Elsevier/North-Holland; 1980. p. 53–79.

McDonald RV, Siegel S. Intra-administration associations and withdrawal symptoms: morphine-elicited morphine withdrawal. Exp Clin Psychopharmacol 2004a;12:3-11.

McDonald RV, Siegel S. The potential role of drug onset cues in drug dependence and withdrawal. Reply to Bardo (2004), Bossert and Shaham (2004), Bouton (2004), and Stewart (2004). Exp Clin Psychopharmacol 2004b;12:23–6.

Mellanby E. Alcohol: its absorption into and disappearance from the blood under different conditions. Special report series, vol. 31. London: Medical Research Committee; 1919.

Peper A. A theory of drug tolerance and dependence I: a conceptual analysis. J Theor Biol 2004a;229:477–90.

Peper A. A theory of drug tolerance and dependence II: the mathematical model. J Theor Biol 2004b;229:491–500.

Poulos CX, Cappell H. Homeostatic theory of drug tolerance: a general model of physiological adaptation. Psychol Rev 1991;98:390–408.

Radlow R. Abstinence and chronic tolerance: a quantitative analysis. Alcohol Clin Exp Res 1993;17:503.

Radlow R. A quantitative theory of acute tolerance to alcohol. Psychopharmacology 1994;114:1–8.

Radlow R, Hurst PM. Temporal relations between blood alcohol concentration and alcohol effect: an experiment with human subjects. Psychopharmacology 1985;85:1–8.

Ramsay DS, Woods SC. Biological consequences of drug administration: implications for acute and chronic tolerance. Psychol Rev 1997;104:170–93.

Rimmele CT. The effect of acute tolerance and rate of alcohol consumption on impairment. M.S. thesis, San Diego State University, San Diego, CA, 1984.

Sdao-Jarvie K, Vogel-Sprott M. Response expectancies affect the acquisition and display of behavioral tolerance to alcohol. Alcohol 1991;8:491–8.

Sdao-Jarvie K, Vogel-Sprott M. Learning alcohol tolerance by mental or physical practice. J Stud Alcohol 1992;53:533–40.

Siegel S. Evidence from rats that morphine tolerance is a learned response. J Comp Physiol Psychol 1975;89:498–506.

Solomon RL, Corbit JD. An opponent-process theory of motivation: I. Temporal dynamics of affect. Psychol Rev 1974;81:119–45.

Stewart J. Disentangling the sources of opioid withdrawal responses. Comment on McDonald and Siegel (2004). Exp Clin Psychopharmacol 2004;12:20–2.

Tampier L, Quintanilla ME. Effect of a dose of ethanol on acute tolerance and ethanol consumption in alcohol drinker (UChB) and non-drinker (UChA) rats. Addict Biol 2002;7:279–84.

Wu PH, Tabakoff B, Szabó G, Hoffman PL. Chronic ethanol exposure results in increased acute functional tolerance in selected lines of HAFT and LAFT mice. Psychopharmacology 2001;155:405–12.