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PERSPECTIVE

Time-dependent sensitization: the odyssey of a scientific heresy from the laboratory to the door of the clinic

SM Antelman, J Levine and S Gershon

Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh, School of Medicine, Pittsburgh, PA 15213, USA

This review provides both a biological and clinical perspective on Time-Dependent Sensitization (TDS), an ancient amplified memory response to threat manifest in the ability of both drugs and nondrug stressors to induce neuronal and behavioral effects which strengthen entirely as a function of the passage of time following even a single or acute exposure. Evidence is presented to show that TDS may be involved in the development of a spectrum of diseases and how drug regimens based on the principles of TDS could provide a novel and revolutionary means of treating psychiatric and other illnesses. *Molecular Psychiatry* (2000) **5,** 350–356.

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'Although I am fully convinced of the truth of the views given in this volume . . ., I by no means expect to convince experienced naturalists whose minds are stocked with a multitude of facts all viewed, during a long course of years, from a point of view directly opposite to mine. . . . [B]ut I look with confidence to the future,—to young and rising naturalists, who will be able to view both sides of the question with impartiality.'

Charles Darwin, '*On the Origin of Species by Means of Natural Selection . . .*'[1]

'A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.'

Max Planck, '*Scientific Autobiography and Other Papers*'[2]

We typically begin lectures on 'Time-Dependent Sensitization (TDS)' by posing the following question: 'If you knew that a drug was given to a human or lower animal for days or weeks before a desired result was observed, how would you interpret this information?' The response, invariably, is that the drug needed to be given over this time period, in order to achieve equilibrium between the blood and target organ. We then point out, that, at least from the standpoint of logic, there is another, equally plausible alternative. Giving the drug once or twice could have triggered a biological process which then progressed entirely as a function of the passage of time, eventually leading to the result obtained, ie, what we have termed TDS.[3] Indeed, without testing and empirically excluding the latter possibility, it is logically impossible to legitimately conclude—as has nevertheless been done in medicine for centuries—that clinical effects observed following chronic drug treatments, in fact require such a regime.

The results of study after study over the last two decades indicate very clearly that the alternative posed is not limited to an exercise in logic, but is demonstrable in a host of biological systems as well as clinically. In fact, TDS has now been demonstrated for so many endpoints and after so many different types of drugs, that it warrants consideration as a general principle of biological functioning. It is important to note that acceptance of TDS does not preclude belief in the specific, pharmacological actions of individual drugs. Rather, TDS is a nonspecific process, which may be common to most drugs. Although, as the ensuing discussion indicates, TDS appears to be a ubiquitous process, this should in no way be misconstrued to mean that we believe it applies or is important for all drug effects or all actions of a given drug. Where relevant, it would apply to the long-term consequences of acute or brief treatment and is not applicable to the more-or-less immediate or very short-term effects of drugs. At this point, we simply do not know enough to say with any certainty which actions of a given agent are likely not to exhibit TDS since comparatively few studies have employed an appropriate protocol. The primary goal of this article is to review accumulating evidence indicating the efficacy of a TDS approach to treatment. We work toward that end by first acquainting the reader with its preclinical foundation.

Correspondence: SM Antelman, PhD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213, USA. E-mail: antelmansm@msx.upmc.edu
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Mostly preclinical findings

In 1980, in papers published in *Nature* and *Science*, this laboratory expressed the heresy that it might not be necessary to prescribe antidepressant treatments according to a conventional, several-times-daily, regime.[4,5] It was suggested instead that the characteristic delay of several weeks in the therapeutic effects of these agents was due to biological changes occurring with the passage of time following acute treatment rather than pharmacokinetic factors and that therefore the drugs could be taken once every week or two and still be as effective as if administered chronically. This audacious proposal was based on the results of single-unit electrophysiological studies of rat midbrain dopamine neurons following both accepted pharmacological and nonpharmacological treatments for depression.

Specifically, we found that acute exposure to either the tricyclic antidepressant (TCA), imipramine, or one very brief electroconvulsive shock (ECS), followed by 7–10 days without treatment, induced a change in the responsivity of dopamine autoreceptors, which grew, ie, sensitized or strengthened, with the passage of time, resulting in neuronal changes that were approximately 30% *greater* than those seen in control groups examined at the same time but exposed to daily drug or ECS.[4,5] These findings were the first to demonstrate that treatments well-established for use in depressive disorders could induce effects which evolve entirely as a function of time and do not require regular administration. Moreover, by virtue of the fact that a single exposure to ECS—still recognized as the most effective means of treating major depression—resulted in the same effect as a drug, a compelling argument could be made that TDS, even when triggered by a drug, does not depend on pharmacokinetics.

When additional antidepressant compounds—the TCAs, amitriptyline and desipramine, the monoamine oxidase inhibitor, phenelzine, the atypical compound, bupropion, and the serotonin reuptake inhibitor, citalopram[6–10]—were later examined using a TDS regimen, results were the same; the effects grew with the passage of time over extended periods. This was true even when different testing procedures (biochemical and behavioral) were employed and other neurotransmitters (serotonin and norepinephrine) were studied.[6,7]

The data described above suggested that TDS was not limited to the structure of an individual compound, the method of examination or the endpoint studied. Indeed, the ECS findings implied that it also goes beyond drugs. In the years since these early studies, their suggestion of the ubiquitous nature of TDS has been well borne out. Thus, the phenomenon has been demonstrated following numerous drugs, differing both in chemical composition and purpose, as well as in a host of bodily systems.

Among drugs (in addition to those already noted)—and chemicals—it has been observed with the stimulants, amphetamine and cocaine,[11–14] anxiolytic, anxiogenic and hypnotic benzodiazepines, ie, diazepam,[15] flumazenil[15] and triazolam,[16–18] ethanol,[19,20] morphine,[21] clenbuterol,[22] clomipramine,[23–25] 2-deoxy-D-glucose,[19] the cytokines, interleukin-1 beta,[26,27] interleukin-2,[28] tumor necrosis factor-alpha,[29] the anxiogenics, FG7142 and pentylenetetrazol,[30,31] estrogen,[32–34] the corticosterone antagonist, metyrapone,[35] corticotropin-releasing hormone antibody,[35] the antipsychotics, haloperidol, fluphenazine and clozapine,[36–39] lipopolysaccharide, an endotoxin[27] and saline.[19]

Systems, structures and other endpoints exhibiting TDS following a single or acute exposure to an appropriate stimulus, include striatal, mesolimbic and mesocortical dopamine pathways, reflected in changes in autoreceptors, postsynaptic receptors, mRNA and turnover,[4,5,13,40–42] both α- and β-noradrenergic receptors,[7,22,31] serotonin,[6] GABA,[15] aspartate,[20] acetylcholine,[43] plasma corticosterone,[26,40,44] cortisol, β-endorphin and ACTH,[14,28] median eminence arginine vasopressin,[26,27,45] glucocorticoid and mineralocorticoid receptor binding in the hippocampus,[45,46] negative glucocorticoid feedback,[47] nitric oxide,[48] serum apolipoproteins,[32] the immune system,[49] brain glycogen[50] and vitellogenin mRNA induction.[33,34]

The diversity of agents capable of inducing TDS and the wealth of endpoints affected, as well as its extremely long-lasting nature (up to at least months after a single stimulus exposure[36]), make it apparent that it does not obey the 'rules' typically associated with pharmacological phenomena. Indeed, in most respects the induction of TDS appears almost antithetical to what we know of drug actions. It shows generality rather than specificity, and grows, ie, strengthens with the passage of time, while drug levels and specific effects on target organs typically decline over time in the absence of further treatment. In short, while it can be induced by drugs, TDS almost certainly reflects nonpharmacological actions of such pharmacological agents.

Unaccustomed though physicians and scientists may be to thinking about drugs as anything other than pharmacological or medicinal agents, a moments reflection should make it obvious that there is another aspect to drugs with potentially enormous implications, that has been ignored completely. It is a fact, not conjecture, that drugs also represent foreign substances to the organism seeing them for the first time or after a long hiatus. Moreover, since the cellular perception of foreignness is always likely to be more or less immediate, while the pharmacological effects of a drug typically take tens of minutes, it seems 'commonsensical' that the foreign aspect of drugs would be dealt with first. Since a foreign stimulus of sufficient intensity would doubtless be perceived as a potential threat to the organism, survival dictates that an adaptive process which develops and sensitizes with time, rather than repeated exposure, be set in motion after even a single encounter with such a stimulus. This ensures that if the organism survives the initial threatening episode it would have a sensitized defensive response, enabling it to react faster and/or more strongly, should it ever reencounter the same or a similar stimulus. We believe that TDS may be such an adaptive process and that its

induction represents a response to the foreign aspect of drugs, rather than their specific pharmacological actions. Evidence clearly supportive of this concept was provided by our finding that the long-term, sensitizing effects of amphetamine on subsequent amphetamine were mimicked both by haloperidol, a drug with an opposite pharmacological profile, which, of course, is also a foreign substance, as well as its vehicle, which is presumably just a foreign substance. Moreover, the combined treatment of amphetamine *plus* haloperidol or its vehicle produced a significantly greater long-term effect than amphetamine alone.[44] These findings are completely inimical to any pharmacological interpretation of the ability of drugs to induce TDS. They suggest that one cannot simply view long-term drug effects as a one-dimensional process, dependent only on the relatively specific pharmacological actions of a given compound.

The reader might object that there are drugs—eg dopamine, norepinephrine, and saline—which also are natural constituents of the body and therefore should not be perceived as foreign. Nevertheless, even with such substances, the volumes likely to be administered, coupled with the mode of administration, eg by injection, would label the agents as foreign. It should also be noted that any abnormal endogenous change in one system will almost certainly be viewed as threatening and therefore foreign by other systems as well. Basically, the rest of the body reacts with the neuronal/hormonal equivalent of asking 'what the hell is going on here?' In other words, foreignness is not simply a consequence of imposing a drug or exogenous nondrug stressor, but also abnormally large endogenous changes, however these are induced.

It is interesting to note, that although it has long been known that host reactions to vaccines or other foreign agents describe a TDS-like process, before our work, no one thought to determine whether the TDS response to foreignness existed outside of the immune system. The work described here suggests that it is true of many and perhaps all bodily systems and that it can be induced by drugs, most of which are too small in molecular weight and complexity to qualify as antigens, and therefore would not be expected to trigger an immune response. This indicates that TDS represents a surveillance system responsive to potential threats to the organism that is more sensitive to foreign substances than is immunological memory. Moreover, the nonspecificity of TDS—as contrasted with the highly specific nature of immunological memory—also suggests that it may have evolved earlier.

Since foreignness, is, by definition, novel, and novelty has been long recognized as stressful to organisms, our view implies that it should be possible to induce TDS as readily by exposing an animal to a nonpharmacological stressor as to a drug. It has now been shown numerous times with a diversity of stressors that this is indeed the case. Among nonchemical stressors, TDS has been induced by seconds of loud bell ringing,[51] food deprivation,[12] tailpinch,[11] shock,[40,45,52] immobilization,[19,49] needle jab,[19] the psychological stimulus of a brief period in a strange environment,[41] brain surgery,[27] a combination of some of the foregoing plus swim stress,[47] and, as noted above, ECS.[4]

The foregoing discussion should not be taken to imply that any life experience, no matter how innocuous or trivial, can induce long-term TDS. This process depends both on the intensity of the stimulus[41]—whether a drug or nondrug stressor—and also on the background level of reactivity of the organism.[53,54] Thus, the same intensity stimulus may have very different effects in animals or humans that differ in level of reactivity.[42]

Another notable aspect of TDS is its bidirectionality. It can manifest as either time-dependent enhancement or inhibition. Intensity of the inducing stimulus plays a key role in determining the direction of TDS, with agents of 'lower' intensity resulting in enhancement and those of 'higher' intensity, diminution in the effects of the same compound. This property of TDS is well-illustrated in a study which compared 'lower' and 'higher'-intensity environmental, metabolic (distinctly different doses of the metabolic stressor, 2-deoxy-D-glucose) and pharmacologic (markedly different doses of ethanol) stressors in terms of their effect on haloperidol catalepsy measured either 1–2 hours or 2 weeks later. Regardless of the type of stressor employed, lower intensity stimuli always enhanced, while those of higher intensity always diminished the influence of haloperidol at the longer, but not the shorter testing period. In other words, both potentiating and inhibiting actions strengthened with the passage of time.[19] Long-term, time-dependent enhancement or inhibition of hippocampal mineralocorticoid and glucocorticoid receptor binding has also been observed following brief exposure to stressful stimuli differing in severity.[46]

Clinical evidence for TDS

Does TDS apply to humans? In other words, can a brief exposure to a drug or other biological intervention induce a clinical effect which grows with the passage of time? If so, how much initial exposure is necessary (ie dose, intensity of biological agent). How long does it take for the effect to develop and how long does it last? Are 'booster' treatments necessary? Do differences exist between diagnostic groups and individuals with regard to the above parameters? While these are all relevant questions, which eventually have to be addressed, due to the limited number of studies which relate to TDS—some of them designed to test other hypotheses—only partial answers can be given at this time.

Although the ability of drugs and nondrug stressors to induce effects which then progress with the passage of time, is referred to in animals as time-dependent sensitization—a name coined by one of us[3]—in humans, the same phenomenon has often been labeled 'pulsed therapy', and the regime employed to implement it, referred to as a 'pulse loading strategy'.[23–25] This has had the unfortunate effect of—at the

very least—dichotomizing what is obviously one phenomenon, as well as failing to inform those unfamiliar with it, of the very strong preclinical foundation that exists. It is hoped that this article will help to remedy this problem and unify the preclinical and clinical data.

Most of the extant literature related to TDS deals with studies on the treatment of depression. These used one of three dosing strategies:

(a) a single loading dose of antidepressants followed by either a no-treatment or placebo phase.
(b) two loading doses given on successive days followed by a no-treatment or placebo phase.
(c) weekly repeated one-day load dose strategy.

As single pulse dose and two successive days pulse dose regimens are closely related, they will be considered as belonging to one category, while the weekly repeated pulse dose approach will be viewed separately.

Five drug studies—most of them administering clomipramine (a selective serotonin reuptake inhibitor) for the treatment of depression—were published using the single, or two loading dose strategies.[23–25,55,56] A sixth study used the single treatment strategy with electroconvulsive therapy (ECT).[57] Despite the fact that only acute treatments were administered, all of these showed statistically significant, clinically meaningful improvement, which grew with the passage of time, suggesting a TDS process.[58] There was no improvement in depression in one study using the one-day loading dose regimen with doxepin, repeated weekly.[59] However, even here, the authors themselves point out that they did obtain evidence of TDS when examining a measure of hypothalamic-pituitary-adrenocortical (HPA) activity.

So that readers can judge the TDS effects for themselves, we present two representative examples of single pulse dose studies, one using pharmacological and the other, biological treatment. The first is that of Dube *et al*.[25] This study had three groups of unipolar depressed patients, all with similar Hamilton Depression Scale Scores (HDS) of between 21 and 24. Group A of 16 subjects received clomipramine (250 mg po) once, followed by placebo treatment for 22 days. Study group B of 11 also received clomipramine once (250 mg po), then placebo for 7 days. A control group of 7 subjects got placebo po in lieu of drug on day one, then continued with placebo for another 7 days. The results for group A showed HDS improvement of 19% at day 3, 29% on day 8, 40.5% on day 15 and 62% on the 23rd and final day of the experiment. Group B, which had only a 1-week withdrawal period after drug, showed a 30% improvement at day 8, essentially identical to the 29% seen in Group A at the same time. The placebo control group actually showed a decline, from 20% at day 3 to only 6.7% improvement at day 8. The results of this study, show very clearly that the antidepressant influence of clomipramine grew entirely as a function of time after only a single administration, reaching a level of improvement typically seen following multiple daily drug treatments over a time-course comparable to that of this study, ie, 3–4 weeks. The latter point is supported by the fact that from days 9–23, group B (and also the control group) received daily clomipramine, reaching an improvement level of 67%, by the last day of treatment, ie, essentially the same degree of betterment seen in Group A after only one treatment.

The second depression study to be described in detail, used ECT and had two groups.[57] An experimental group of 12 depressed patients received a single ECT, followed by five sham sessions on alternate days. An equal number of controls were exposed to ECT a total of six times on alternate days. Baseline HDS was 26 for the study group and 27 for controls. At day 3, experimentals showed 15% improvement in HDS, which progressed as time passed to 30% at day 5, 39% at day 7, 64% on day 9, 73% on the 11th day and 84% on the 13th and last day. The same pattern was observed in the alternate-day ECT controls: 17%-day 3, 21%-day 5, 40%-day 7, 69%-day 9, 73%-day 11, and 79%-day 13. As with clomipramine, the antidepressant effect of a single ECT, grew, ie sensitized, with the passage of time, resulting in the same degree of improvement as the multiple treatment group.

Our analysis shows clearly that a single pulse-dose regimen triggered a process of clinical improvement which grew with the passage of time. If outcome were related to plasma pharmacokinetics, the opposite—ie, a decline in clinical response over time—would have been predicted, since drug levels decrease with time. Similarly, drugs typically exhibit a progressive dissociation from the receptors to which they bind—ie, the binding would decrease with time—and thus receptor binding could not possibly explain an effect, TDS, which strengthens with time. The fact that ECT—a nondrug stressor—also showed TDS (as it did in animals) buttresses the argument against any pharmacokinetic interpretation of the data and instead reinforces the central role of stress in this phenomenon, discussed in the introduction.

Timing of drug treatments appears to be as important in humans as it is in animals, since Deuschle, who used repeated pulse-dosing regimes, generally did not find evidence for TDS. Although, even in this instance, as noted above, an effect was seen on an index of HPA activity, suggesting that there is probably a hierarchy in terms of system vulnerability to manifesting TDS and that only the most sensitive systems are likely to exhibit time-dependent effects with multiple dosing regimes. In other words, different systems or endpoints may differ in optimal interdrug intervals for TDS. TDS is a phenomenon in which less is better.

Although we have so far discussed clinical evidence for TDS only in relation to the therapeutic effects of antidepressant treatments, supporting data also exist for other types of drugs, representing neuroleptics, hypnotics and cytokines. Williams *et al*[39] found a potentiation of cognitive and psychomotor performance impairment in normal volunteers following two

doses of the neuroleptic, haloperidol, administered more than 3 weeks apart and attributed their result to 'time-dependent sensitization.' Kroboth and colleagues (in three separate studies)[16–18] examined normal volunteers following an iv dose of the benzodiazepine hypnotic, triazolam—a drug with an extremely short half-life—administered at 6-day intervals and found that psychomotor impairments increased with the passage of time. They too, attributed their results to TDS. Denicoff *et al*[28] studied plasma beta endorphin, ACTH and cortisol in melanoma patients following the cytokine, interleukin-2, administered in treatment phases separated by 6 days to 3 months. β-endorphin levels were about 10-fold higher and ACTH levels 20-fold higher in the second treatment phase relative to the first. No indication was found that the administered interleukin had persisted in tissues from one treatment course to another and again the effect was explained in terms of TDS. Most interestingly, the authors found that 'Within a treatment phase, repeated administration of IL-2 tends, if anything, to be associated with a progressively diminished hormonal response of cortisol, ACTH, and β-endorphin. *Thus, presumably, the cessation of treatment is necessary to observe the subsequent enhanced increase in hormonal response to IL-2 . . .*' (Italics ours). The studies summarized in this paragraph suggest strongly that TDS is as ubiquitous a process in humans as it is in animals and that it relates to the untoward effects of drugs as well as to their therapeutic actions.

Discussion

While the concept of TDS is undoubtedly quite revolutionary enough for many, and far too iconoclastic for others, some of its possible implications could be viewed as even more startling than the phenomenon itself. For instance, there is evidence to suggest that—at least in some instances—TDS could actually persist across generations although the triggering stimulus is no longer present. This is seen in the endurance across 10 generations of daughter cells of the memory response of human hepatocarcinoma cells to a single transient exposure to estrogen.[32] It is also very strongly indicated by consideration of a TDS-like genetic phenomenon referred to as 'anticipation', in which certain diseases—ranging from the extremes of proliferation to degeneration—have been shown to develop earlier and with greater severity in subsequent generations.[60,61] In short, their effects seem to grow with the passage of time—*intergenerational time*. These findings and the long-lasting nature of TDS point to genetic involvement in this phenomenon. While anticipation appears to follow a TDS-like course, this should not be taken to mean that its cellular manifestation—expanded trinucleotide repeats—is likely to reflect the mechanism of TDS, which is presently unknown.

Although this paper has dealt principally with TDS as it might relate to the treatment of disease, Anticipation suggests that TDS may also describe the process by which many diseases develop. Time-dependent development of PTSD following exposure to even a single traumatic event is by now well-known.[38,62–64] It is similarly believed by dermatologists, for example, that an acute severe sunburn in one's youth can lead to malignant melanoma decades later[65] and that the disease is more likely following intermittent than continuous exposure to the sun.[65] Interestingly, occupational exposure, which would be more or less continuous, actually has been shown to reduce the risk of malignant melanoma.[65] These findings parallel the IL-2 data described above.[28] Time-dependent effects also appear to exist for different types of cancers and other diseases, which frequently—indeed, often typically—take years and perhaps decades to develop after acute exposure to industrial or other toxins. In many of these instances, it would be hard to argue that the offending or inducing agent persisted throughout the period of disease development. This seems to be the case in a number of viral-related diseases, where the viruses act 'only as triggering factors of a pathological process that fuels itself with no further participation of the causal agent'.[66] It is likewise true with phobias, which typically worsen with the passage of time. Referring to the time course of phobia development, Marks[67] states: 'The clinical problem often starts not straight after the trauma but only after a delay of a few days, and may take years to reach full intensity. What is happening during the incubating phase after the trauma? The process may be a form of sensitization.' Failure to consider the possibility that acute exposure to a toxin which then disappears from the body, could lead to the time-dependent development of a disease process which manifests itself only years later, has, for example, been a major stumbling block in understanding many of the illnesses which seem to have developed as a consequence of toxin exposure during the Gulf and Vietnam wars. Relevant to the foregoing, it is notable that Gajdusek (awarded the Nobel Prize in 1976), struggling to understand the puzzle of Kuru, wrote in a 1957 letter: 'or it means that a most unusual toxin exposure is involved, one in which exposure months or even years previously is sufficient to initiate a progressive slow neurological destruction'.[61]

The implications of TDS induced by drugs, nondrug stressors, and interactions between them, are many and profound. At the top of this list is the very real possibility that, to paraphrase the title of an article we wrote more than a decade ago,[9] drugs may have been given the wrong way for centuries. The clinical evidence for TDS reviewed here, supports strongly our suggestion of almost 20 years ago,[4,5] that instead of managing disorders such as depression by multiple daily drug treatments, it may be possible to accomplish the same ends by treating once every few weeks. While results thus far have been extremely encouraging, obviously many more clinical studies need to be carried out before our hypothesis of the clinical utility of employing a TDS regime can be accepted as proven. Nevertheless, and despite the fact that we do not know the mechanisms underlying TDS, the advantages of employing such a regime are potentially enormous, both in terms of

likely patient compliance and cost savings to the patient, health-care delivery systems and third-party payers such as HMOs. Moreover, there are additional—indeed, more important—benefits which might be gained from using a TDS strategy. As we have shown in animals,[49] a single exposure to a stressor (eg an appropriate drug) several weeks earlier might sensitize the immune system to the suppressive influence of agents used to prevent rejection of transplants, thereby permitting reduction in their dosage. To say that widespread adoption of a TDS approach to treating disease would significantly alter the practice of medicine, is almost certainly an understatement. Yet, despite its promise and the ease with which it could be instituted, we are not at all hopeful that this is likely to happen any time soon, if ever. The problem, to quote Keynes,[68] is that: '*The ideas which are here expressed so laboriously are extremely simple and should be obvious. The difficulty lies, not in the new ideas, but in escaping from the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds*.'

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